THE PLANT ALKALOIDS

BELLADONNA PLANTS.

THE
PLANT ALKALOIDS

BY

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SECOND EDITION

WITH 8 PLATES

PREFACE TO THE FIRST EDITION

IN certain respects the plant alkaloids rank among the most interesting of naturally occurring substances. For the most part they are of complex structure, so that the determination of their constitution and the discovery of methods of producing them synthetically offer attractive problems to the chemist ; and though a great deal has been accomplished, much still remains to be done in this direction. Their mode of origin and their function in plants are still unknown, and these two questions, with the more important one of correlating the structure of the alkaloids with their physiological action, form still almost untouched fields for combined work on the part of physiologists and chemists. Many of the alkaloids are of great importance in medicine, and the manufacture of these alkaloids and of products containing them constitutes an important branch of the " fine chemical " industry.

In compiling this volume the author has kept in view these various aspects of the subject, and the articles on all the more important alkaloids describe not only the properties and the chemistry of these products, but also their occurrence, methods of estimation, and physiological action. In most cases the original memoirs have been consulted, and references to these are given in footnotes, but for descriptions of the physiological action of the better-known alkaloids Professor Cushny's " Textbook of Pharmacology and Therapeutics " has been largely utilised. The chemical nomenclature and the system of abbreviations used are, with a few unimportant exceptions, those employed in the " Abstracts " published by the Chemical Society of London, with which most English-speaking chemists are familiar.
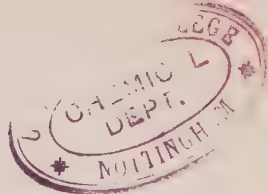
For much laborious work in checking formulæ and references and in reading proofs, the author is indebted to Mrs. Henry, B.A., B.Sc. (Lond.), and to Miss A. Holmes, B.A. (Lond.).

PREFACE TO THE SECOND EDITION

In the decade which has elapsed since the issue of the first edition of this book, the results of much new work on alkaloids have been published, and the inclusion of these has involved re-writing much of the text. It has been possible to incorporate this new material without increasing the size of the book, because the new work has resulted in the determination of the constitution of many alkaloids, and this lends itself to simplification in treatment. Less space is now also devoted to methods of estimation, since this subject is amply dealt with elsewhere in readily accessible form. On the other hand, more attention has been given to such information as is available on the correlation of chemical constitution and pharmacological action among the alkaloids, a subject on which, up to the present, many observations have been made, but from which general conclusions cannot yet be drawn. A few illustrations of some of the more important drugs have been included merely as a reminder that alkaloids have a natural origin, a point chemists often overlook, and that the problems of their origin in plants and their function there are still largely unsolved.

The author takes this opportunity of thanking the Council of the Chemical Society for permission to reproduce a number of graphic formulæ, singly or in groups, from the pages of their publications, a concession which has saved a good deal of labour in transcribing and setting up formulæ. To Professor H. G. Greenish thanks are due for so kindly allowing the inclusion of some illustrations from his " Text-book of Materia Medica." The author is again greatly indebted to Mrs. Henry, B.A., B.Sc., for much assistance in checking formulæ and correcting proofs, and to Mr. H. Paget, B.A., and Mr. W. H. Gray, B.Sc., for similar help in proof-reading.

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THE PLANT ALKALOIDS

INTRODUCTION

THE word " alkaloid " was at first used to describe all organic bases, including the natural alkali-like substances, which occur in plants. When this name was introduced, comparatively few of these were known and they were all alike in possessing basic properties and in exhibiting physiological activity. These two characteristics, in conjunction with their complex structure, made it possible to regard them as forming a well-differentiated group of chemical compounds, but later work showed that there were also present in plants such simple bases as ammonia and methylamine, and substances that contained nitrogen, and were yet acidic rather than basic. Further, complex substances closely related to typical alkaloids but devoid of marked physiological action, became known. All this was confusing to systematists, and Königs proposed to restore definiteness to the use of the term by restricting it to naturally occurring pyridine compounds, but this ruled out such important substances as the purine and glyoxaline derivatives, and could not be accepted as a satisfactory use of the name. The term " alkaloid " is now generally understood as meaning a relatively complex basic substance occurring naturally, and possessing some physiological action, and it will be used in that sense in this volume.

Certain basic substances are common to plants and animals, and there is no logical ground for the separate treatment of " vegetable alkaloids " and " animal alkaloids," but most of what used to be known as animal alkaloids are simpler than, and different in type from, the majority of the vegetable alkaloids and they are even more difficult to isolate in a pure state and to investigate. Further, the literature relating to them has grown rapidly in recent years, and their investigation has developed on special lines, so that for practical purposes the bases of animal origin can be dealt with most conveniently as a separate class, and in this volume only alkaloids derived from plants will be considered.

A number of comparatively simple amino-substances—such as asparagine—has been recorded as occurring in plant seedlings. These substances can scarcely be classed as alkaloids, and, as they

are dealt with in general text-books on organic chemistry, they are not referred to except incidentally in this volume.

Classification of Alkaloids

The chemistry of alkaloids dates from 1817, when Sertürner discovered a crystalline, salt-forming, physiologically active substance, morphine, in opium. This was followed by Robiquet's isolation of narcotine in the same year, and in the following year Pelletier and Caventou prepared strychnine. Since then the number of such substances has been added to every year. Much is now known regarding the structure of most of the more important alkaloids, some syntheses have been effected, and there is no longer any doubt that many of them are closely related and have a common nucleus. It should be possible, therefore, to classify alkaloids according to their nuclear structure, but no sooner is a system of classification adopted than it becomes obsolete by the discovery of new data, and this difficulty will remain until the subject is no longer of interest to investigators. For text-book purposes, however, some kind of systematic arrangement must be adopted, and in this volume the subject-matter will be divided as follows :

Group.	Nucleus.	Examples.
1	Pyrrole . . .	Hygrine, stachydrine
2	Pyridine . . .	Coniine, nicotine
3	Tropane . . .	Atropine, cocaine
4	Quinoline . . .	Quinine, strychnine
5	*iso*Quinoline . .	Papaverine, narcotine
6	Indole . . .	Harmine
7	Glyoxaline . . .	Pilocarpine
8	Purine . . .	Caffeine, theobromine
9	Alkaloids derived from aliphatic amines (non-heterocyclic group) .	Damascenine, hordenine
10	Alkaloids of unknown constitution . .	Aconitine, emetine

It is difficult to say anything for such a classification except that it is expedient. It begs questions in every direction. Thus nicotine, which is classified as a pyridine derivative, also contains a pyrrole nucleus, whilst cocaine and atropine, which can be regarded as derived from both pyridine and pyrrole, are grouped separately

from the derivatives of either. Quinine and strychnine are classed by long custom as quinoline derivatives when each might reasonably be placed in a new group, and no place is found for sparteine, which, according to the formula accepted for it, belongs to a quinuclidine group, which might also contain quinine and its allies. The attitude of a chemist towards this, or any similar system of classifying alkaloids, should be that of a modern botanist towards the Linnean system of classifying plants—it should strike him as convenient but unnatural. It is only necessary to bring together a series of formulæ of typical alkaloids to see that there already exists the beginnings of a system in which the classification will be natural, *i.e.*, in which clear developmental relationships will be traceable between the simplest and the most complex structures. Such a system would be satisfactory to a chemist, and there is plenty of evidence that it would be sound biologically. In any plant species in which a number of alkaloids occur, it is almost invariably the case that these are closely related and can be regarded as marking stages in development. Thus the researches of Späth and his collaborators have made it possible to formulate part of the interesting series of alkaloids obtainable from mescal buttons in the following way :
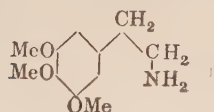
Mezcaline
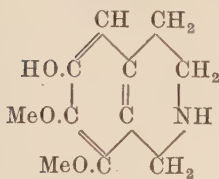
Anhalamine
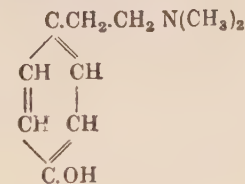
Hordenine
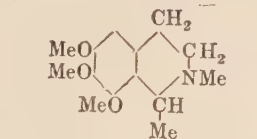
Pellotine O-methyl ether

Similarly, in the *iso*quinoline series, some of the numerous conversions and syntheses that have been effected can be represented by a general diagram, and the existence in the same or closely related plants of a number of the alkaloids concerned adds biological interest to this illustration. Taking 1-benzyl*iso*quinoline, of which papaverine and laudanosine are simple derivatives, the insertion of a lactone ring between the points *a* and *a'* produces 1-meconyl*iso*quinoline, of which narcotine and narceine are simple derivatives.

In the same structure the formation of a link from a to c gives rise to the nuclear structure common to glaucine and *iso*thebaine, and
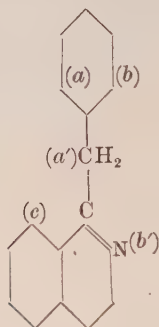
I *Benzyl*iso*quinoline.*

potentially present in morphine, codeine and thebaine. These, with the exception of glaucine and *iso*thebaine, are alkaloids of opium, whilst *iso*thebaine occurs in a plant of the same genus as the opium poppy and *Glaucium flavum*, the source of glaucine, is closely allied and belongs to the same natural order. From the same primary structure by the insertion of a single carbon linkage from b to b', the nucleus is formed from which berberine and corydaline, with some of its associated alkaloids, can be regarded as derived, and from this, in turn, by a further step the characteristic central structure of the alkaloids protopine and cryptopine found in opium can be derived, and this step has also been achieved in the laboratory.

These changes can be succinctly summarised thus :

*ISO*QUINOLINE ALKALOIDS

	→Type II.	Narcotine, narceine, hydrastine
Type I.	→Type III.	Glaucine, *iso*thebaine, apomorphine
(Papaverine)	→Type IV.	Berberine, corydaline
	↓	
	Type V.	Cryptopine

When it is possible to treat every group of alkaloids in this fashion it may be desirable for compilers to arrange the subject-matter of a book of this kind in a natural sequence, beginning with the simplest plant base and ending with the most complex, but, in the present state of knowledge, the most practical plan appears to be to use a group system such as that outlined above and to modify it by treat-

ing all the alkaloids derived from one plant together. It thus happens that the alkaloids of pomegranate root bark are discussed in the pyridine group because the principal alkaloid of the set is of that type, but it includes pseudopelletierine, derived from a base which can be regarded as a ring homologue of tropane.

In the first nine groups are included all the alkaloids to which constitutional formulæ have been definitely assigned. To the tenth group have been relegated all the others, irrespective of the fact that the type of nucleus present in some of them is known, *e.g.*, it seems likely that the ipecacuanha alkaloids are *iso*quinoline derivatives, and the Calabar bean alkaloids probably have an indole nucleus.

Physical Properties

Most of the alkaloids are colourless, crystalline substances, containing carbon, hydrogen, oxygen, and nitrogen, but a few are liquid, and these are generally free from oxygen and are more or less readily volatile.

Comparatively few of them are coloured : berberine and dehydro-corydaline are yellow, but furnish on reduction colourless tetra-hydrides. A few of the alkaloids are themselves colourless, but yield coloured salts : thus the colourless sanguinarine gives red salts.

Many of the alkaloids show characteristic absorption spectra, due to the unreduced portions of their molecules, and this property has been successfully used by Dobbie and his collaborators in settling various knotty points in the constitution of some of the more complex alkaloids. Most of the alkaloids are optically active, and in a few cases, *e.g.*, the aconitines and narcotine, the salts show an optical activity opposite to that of the free alkaloid. In some instances, notably hyoscine, investigation of the optical relations of the alkaloid and its derivatives has led to important results, bearing on the constitution of the parent base. The optically active alkaloids have frequently been used in deracemising acids, since they often form sparingly soluble salts, which are readily separated into their optical antipodes by fractional crystallisation.

Chemical Properties

In order to obtain a satisfactory idea of the chemical properties of the alkaloids as a class, it would be necessary to discuss in some detail a typical member of each of the first nine groups referred to in the scheme of classification already given, and as this is done in

the special sections relating to these groups, it need not be repeated here.[1] It is necessary, however, to refer in a general way to the chemical characteristics of the alkaloids in so far as these affect their isolation, purification, detection and estimation. For a fuller discussion of these subjects, which are of special importance in analytical work connected with alkaloids, the introductory article on alkaloids in Allen's "Organic Analysis," should be consulted.

PREPARATION.—In isolating alkaloids from plants, advantage is taken of the fact that they generally occur in the form of salts, which are soluble in alcohol or in water. In the comparatively rare cases in which they occur in the free state they may, as a rule, be extracted by alcohol, chloroform, or ether, or in some cases by light petroleum. When present in the form of salts insoluble in alcohol, they may be obtained by mixing the ground plant with lime or magnesia and then extracting with one of the solvents already named. In such cases, extraction with alcohol or water, slightly acidified, may also be resorted to. When it is necessary to concentrate extraction liquors containing alkaloids by heating, this should be done under reduced pressure, in order to avoid risk of decomposition. From the concentrated liquors fat, resin, and other matters are generally removed by adding water, or, if necessary, very dilute acid to keep the alkaloid in solution. This aqueous or acid solution may then be shaken with an immiscible solvent to remove colouring-matter, etc., but care must be taken that the alkaloid is not also removed by the solvents used, since some weak bases can be removed from acid solution by indifferent solvents. The concentrated liquid is then made alkaline, a weak alkali—such as dilute ammonia, sodium carbonate, or sodium hydrogen carbonate solution—being used in preference to solutions of alkali hydroxides, though the latter are sometimes necessary to keep phenolic bases in solution for subsequent extraction, and to liberate strongly basic alkaloids. Most of the alkaloids are precipitated by this treatment, and may then be separated by shaking out with chloroform, ether, or other suitable solvent. Certain alkaloids are soluble in water in all proportions and are not removed from water by immiscible solvents. In such cases treatment of the liquors with one of the precipitants mentioned

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[1] For typical instances of the work involved in determining the constitution of alkaloids, the papers by Perkin, Robinson and collaborators referred to in the sections on berberine, cryptopine, and harmine should be consulted.

below may be resorted to and the alkaloid recovered from the washed precipitate. Examples of these methods of preparation and references to other processes will be found in the special sections of this volume, but mention may be made more especially of the methods described under aconitine (p. 355), solanaceous alkaloids (p. 62), strychnine (p. 180), and the opium alkaloids (p. 259). For the isolation of volatile alkaloids, the sections on nicotine (p. 51) and coniine (p. 30), should be consulted.

The " total alkaloid " having been isolated from a plant, it is necessary to ascertain whether it consists of a single substance, and, if it is a mixture, to separate it into its constituents. If separation into phenolic and non-phenolic bases has not been effected in the preliminary work, the total alkaloid may be re-dissolved in dilute acid, slight excess of a dilute solution of caustic alkali added, and the non-phenolic base or bases extracted by a suitable solvent. When no more or only traces of alkaloid are removed, the solution should be again acidified, sodium carbonate added in slight excess, and the phenolic bases extracted. For separation of the components in a pure state, fractional crystallisation of the mixture from suitable solvents must be resorted to. Where small quantities of an alkaloid crystallising with difficulty are concerned, it is sometimes useful to dissolve the material in a suitable solvent, and then add, drop by drop, a second medium in which the alkaloid is sparingly soluble, until the liquid becomes cloudy. On standing, crystals may be deposited ; if not, the clear liquid is poured off and the treatment repeated. To avoid change in the composition of the mixed solvent, this process should be conducted in stoppered bottles. The purification of an alkaloid is usually greatly facilitated by converting it into a salt. For this purpose the haloid salts are generally better suited than the sulphates or nitrates, and other useful salts are the oxalates, picrolonates, picrates and sometimes the aurichlorides and platinichlorides. The method of fractionation referred to above is also applicable to alkaloidal salts, the dry substance being dissolved in dry alcohol, and dry ether or acetone added, drop by drop, till a faint cloudiness appears.

For the identification of an alkaloid the usual means adopted for organic compounds, viz., determination of the melting-point or some other physical constant for the free alkaloid and for one or more of its derivatives, should be used. Colour reactions, which are frequently used for this purpose, are unsatisfactory and often due to impurities, and when they have to be used should finally be applied, side by

side, to the substance under examination and to a pure specimen of the alkaloid.

ESTIMATION OF ALKALOIDS IN PLANTS.—The estimation of alkaloids in plants involves their complete extraction on the lines just described, and their separation in a form in which they can be weighed or titrated. Typical methods of estimation are described under opium (p. 255), cinchona (p. 127), cocoa (p. 333) and solanaceous drugs (p. 65).

It should be remembered in titrating alkaloids that some of them are indifferent to some indicators, so that their salts behave like a corresponding quantity of free acid, others are monoacidic to one indicator and diacidic to another, whilst most of them give unsatisfactory end-reactions with some indicators.

Precipitants

One of the most characteristic properties of alkaloids is that of forming complex double salts with certain metallic haloids. These double salts are generally nearly insoluble in water, so that mere traces can be detected by their formation. The following are a few of the most useful precipitants of this kind.

AURIC CHLORIDE.—A solution of auric chloride gives yellow or orange-coloured precipitates (aurichlorides) with many alkaloids dissolved in a slight excess of dilute hydrochloric acid. As a rule, the precipitates can be recrystallised from alcohol or water containing a little hydrochloric acid. They have the general composition $B.HCl.AuCl_3$, but compounds of the type, $B.AuCl_3$, are also sometimes produced, and under certain conditions aurichlor-derivatives, containing the group $AuCl_2$ in place of a hydrogen atom of the alkaloid, are formed. Examples of such compounds are referred to under japaconitine (p. 362) and caffeine (p. 331). The aurichlorides of the solanaceous alkaloids are especially useful in separating and characterising the members of this group.

PLATINIC CHLORIDE.—Similar compounds, the platinichlorides, $(B.HCl)_2.PtCl_4$ or $B.H_2PtCl_6$, in the case of diacidic alkaloids, are formed with platinic chloride, but as a rule these are more soluble than the aurichlorides, especially in dilute hydrochloric acid.

MERCURIC CHLORIDE.—With solutions of this salt many of the alkaloids give characteristic, crystalline mercurichlorides of the general composition, $B.HCl.HgCl_2$.

Among other precipitants of this class may be mentioned ferric chloride, lead tetrachloride, telluric and thallic chlorides.

Solutions of certain double metallic haloids form the best-known group of alkaloidal precipitants and include the reagents most commonly used for detecting their presence. Among these are the following :

POTASSIUM MERCURIC IODIDE (MAYER'S REAGENT).—This is best prepared by adding 6·8 grm. of mercuric chloride, dissolved in water, to 25 grm. of potassium iodide, dissolved in water, and diluting to 1000 c.c. This solution gives white curdy precipitates with minute traces of alkaloids in solutions slightly acidified with hydrochloric or sulphuric acid. The precipitates vary in composition with the conditions of precipitation. The alkaloids may be recovered from these precipitates by suspending them in water and passing a current of sulphuretted hydrogen, when the alkaloidal hydriodide is formed, and may be recovered by concentrating the filtrate.

Similar precipitates are afforded by solutions of potassium bismuth iodide (Dragendorff's reagent), potassium cadmium iodide (Marmé's reagent), iodine in potassium iodide (Wagner's reagent) and other like solutions.

In addition to the foregoing precipitants, which give insoluble complex double salts with the alkaloids, a number of acids form insoluble alkaloidal salts and therefore act as precipitants.

GALLOTANNIC ACID.—A solution of gallotannic acid gives precipitates of the corresponding tannates with most alkaloids in neutral solution. These precipitates are generally soluble in ammonia and sometimes in dilute acids.

PICRIC ACID (HAGER'S REAGENT).—The picrates of most of the alkaloids are sparingly soluble in water or dilute acids, and are precipitated when a cold, saturated, aqueous solution of picric acid is added to a solution of an alkaloidal salt. They can usually be recrystallised from alcohol and are often characteristic.

PHOSPHOMOLYBDIC ACID (SONNENSCHEIN'S REAGENT).—A solution of this substance gives amorphous yellow precipitates with many alkaloids, and may be used for separating them from associated non-alkaloidal organic matter, since the alkaloids may be regenerated by treating the precipitates with sodium carbonate and extracting rapidly with alcohol.

Phosphotungstic acid and metatungstic acid have been also used as alkaloidal precipitants.

Biological Significance of Alkaloids

Alkaloids have been found in comparatively few natural orders of plants : the Ranunculaceæ, Rubiaceæ, Papaveraceæ, Fumariaceæ, Solanaceæ, Leguminosæ and Apocynaceæ are typically rich, and the Rosaceæ, Graminaceæ, and Labiatæ typically poor in these constituents, whilst the Compositæ occupy an intermediate position.

The alkaloids found in a natural order, and especially in any one genus, are usually somewhat closely related : thus the various aconitines are found only in members of the genus Aconitum, which is somewhat remarkable in yielding a new species of aconitine for each new species examined, though all the aconitines appear to be closely related. In some cases a single alkaloid is almost characteristic of an order, e.g., protopine occurs in many plants of the order Papaveraceæ, and of the closely related order, Fumariaceæ. The purine alkaloids, on the contrary, furnish an instance of closely-related alkaloids occurring in plants belonging to widely different orders.

The phanerogams, or flowering plants, are richer in alkaloids than the cryptogams or so-called flowerless plants, and of the former class the sub-class dicotyledons is richer in alkaloids than the monocotyledons.

In comparatively few cases have investigations been made of all parts of a plant for alkaloids, but where this has been done, as in the cases of hemlock, poppy, and some of the solanaceous plants, it has been found that alkaloids usually occur in all parts of the plant. It is generally impossible to say with certainty that one particular part of a plant is always richer than another in alkaloids, since the richness of each part varies with the season and with the condition of the plant. Thus in the case of belladonna, the amounts of " total alkaloid " recorded vary from 0·15 to 0·60 per cent. in the roots, and from 0·05 to 0·64 per cent. in the leaves. The quantity of alkaloid can be increased by special cultivation and especially by selection for richness in alkaloid ; thus the average quinine content in Java cinchona bark has risen considerably as a result of these two processes.

A great deal of discussion has taken place regarding the mode of formation and the function of alkaloids in plants. The discussion on both questions has been mostly speculative, and there are comparatively few experimental data available on either. Many of the simpler substances included among the alkaloids are undoubtedly products of the decomposition of proteins, and this is now generally

believed to be one of the methods by which alkaloids are produced in nature. Kerbosch has brought forward evidence of the formation of narcotine from protein during the germination of poppy seeds, but much more work on the biological side is needed to establish this view of the origin of alkaloids.

It has also been pointed out that pyridine derivatives are produced by the action of ammonia on pyrones, that organic acids and aldehydes, which are either pyrone derivatives or are easily converted into such substances, are of common occurrence in plants : and that by the action of ammonia these substances might be converted into pyridine compounds in nature.

Pictet, who suggested that the precursors of alkaloids are the nitrogenous decomposition products of more complex substances, such as proteins, arising in the ordinary processes of metabolism, supposes that these decomposition products are rendered harmless by the plant in various ways, but more especially by methylation by the action of formaldehyde. On this view, alkaloids containing the pyrrole or indole group are probably protein decomposition products whilst those containing a pyridine nucleus are conceivably produced by the further change of an alkylated pyrrole into pyridine. Pictet had previously demonstrated the possibility of such a change by showing that 1-methylpyrrole, 1-methylindole, and methylphthalimide can be converted respectively into pyridine, quinoline, and *iso*-quinoline by the action of heat. In support of this theory, Pictet and Court have since shown that tobacco, pepper, carrot leaves, coca, and parsley all yield volatile pyrrole bases, probably derived from proteins. Winterstein and Trier [1] have critically examined Pictet's hypothesis, and have themselves suggested that such decomposition products of the proteins as lysine and arginine are raw materials for alkaloidal syntheses in plants, and their views receive some support from Ciamician and Ravenna's experiments, which show that, whilst inoculation of plants with pyridine or pyrrolidine derivatives produces scarcely any increase in alkaloidal content, similar application of dextrose or asparagine causes a considerable increase.

Starting with the same views as to initial materials, Robinson has elaborated a scheme, which suggests plausible reactions whereby the synthesis in plants of all the more important types of alkaloids could take place. It involves, apart from such reactions as methylation, methylenation, reduction, oxidation, and dehydration, all of

[1] *Die Alkaloide*, Berlin, 1910.

which are known to occur in plants, two types of condensation to provide for the linking up of carbon to carbon in the building up of the alkaloids. These are the aldol condensation and the similar condensation of carbinol-amines containing the group $.\dot{C}(OH).N:$ with substances containing the group $.\dot{C}H.CO.$ Robinson works out the possible syntheses of a number of pyrrolidine bases in three stages from ornithine as a starting point.

Stage I.—Oxidation and methylation of ornithine by formaldehyde to a carbinol-amine of the pyrrolidine series.

$$NH_2.CH_2.CH_2.CH_2.CH(NH_2).COOH + H.CHO \longrightarrow$$

$$NH_2 + CO_2 + NHMe.CH_2.CH_2.CHO \longrightarrow \begin{array}{c} CH_2.CH_2 \\ | \qquad\quad >CH.OH \\ CH_2.NMe \end{array}$$
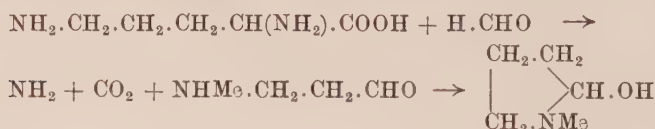
Stage II.—Condensation of the carbinol-amine with acetone-dicarboxylic acid.

$$+ \begin{array}{c} COOH \\ | \\ CH_2.CO.CH_2.COOH \end{array} \longrightarrow \begin{array}{c} CH_2-CH_2 \\ | \qquad\quad >CH.CH(COOH).CO.CH_2.COOH \\ CH_2-NMe \end{array}$$
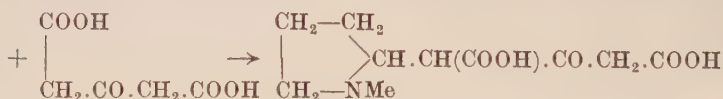
Stage III.—Decarboxylation of the condensation product to (in this case) hygrine

$$\begin{array}{c} CH_2-NMe \\ | \qquad\quad >CH.CH_2.CO.CH_3 \\ CH_2-CH_2 \end{array}$$
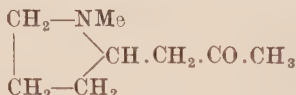
By a similar condensation of two molecules of the carbinolamine with one molecule of acetonedicarboxylic acid, a base isomeric with cuskhygrine would be produced, whilst, if Stage I. is carried a step further, ornithine might yield succindialdehyde and methylamine, thus :

$$NH_2.CH_2.CH_2.CH_2.CH(NH_2).COOH + 2H.CHO \longrightarrow$$
$$2NH_2.CH_3 + CO_2 + CHO.CH_2.CH_2.CHO$$
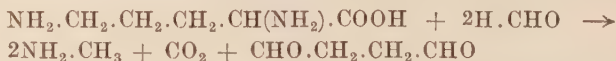
and from these two substances and acetonedicarboxylic acid, Robinson has shown that tropinone can be produced in the laboratory, and tropinone is a probable intermediate in the production of tropine and eventually of hyoscyamine in the plant.

With lysine, the next higher homologue of ornithine as a starting-point, it is possible by a similar series of reactions, to account for the production of methylpelletierine (p. 41) and pseudopelletierine (p. 44).

Similar ideas are ingeniously applied to explain the formation of (1) the quinuclidine system, which occurs in sparteine and the cinchona alkaloids ; (2) the four chief types of *iso*quinoline alkaloids to which reference is made above, and (3) the quinoline half of the cinchona alkaloids ; quinic acid, which occurs in cinchona bark, being suggested as the initial material used by the plant for the last-mentioned synthesis.

This paper formulates, for the first time in considerable detail, a reasonable scheme whereby alkaloids could be synthesised in plants and should give rise not only to efforts to realise such syntheses in the laboratory, but should direct renewed attention to the investigation of plant constituents, since only in this way is evidence likely to be obtained of the actual course of alkaloid formation in plants. Evidence of this kind is at present singularly scarce.

So far reference has only been made to the possibility of the formation of alkaloids in plants from what are comparatively complex materials. Baly and Heilbron claim that they have effected a photosynthesis of pyridine, piperidine and an alkaloid, which may be coniine, by passing carbon dioxide through solutions of potassium nitrate or nitrite exposed to ultra-violet light. Since these conditions at least simulate those under which plants can live, it seems possible that the phytosynthesis of alkaloids may occur in similar direct fashion from carbon dioxide and nitrates. The evidence for the production of coniine in these experiments is not yet as conclusive as might be wished and part of it has been critically reviewed and pronounced insufficient by Snow and Stone. These results have an important bearing on the question of the function of alkaloids in plants. Three views have been held on this subject : (1) That the alkaloids are nutritive materials used by the plant in metabolism ; (2) that they act as protective materials against attack of the plants by animals ; (3) that they are end products of metabolism rendered harmless to the plant and stored for the most part in special cells where they are not readily re-absorbed into the active plant tissues.

The third view is that now generally held, and, though some recent work affords support to the view that alkaloids are plastic materials used in plant metabolism, Annett's work on the formation of alkaloids in the opium poppy in India indicates that in this species, at any rate, the alkaloids are waste products, and the opium poppy is a typical alkaloid-producing plant.

If alkaloids are formed in plants from simple materials in such

a direct way as is suggested by the results of Baly and Heilbron's experiments, it would seem clear that they cannot be waste products. Robinson's views as to the origin of alkaloids, on the contrary, are in harmony with the current belief that they are waste products, and it should be noted that Robinson has produced some confirmatory evidence for his suggestions by a simple and elegant synthesis of tropinone by methods, which certainly could occur in a plant, and his observation does not stand alone, since Wellisch, proceeding on similar but less well-defined lines, has also elaborated schemes for phytosynthesis of alkaloids and has to some extent substantiated his views by appropriate syntheses of substances resembling alkaloids.

Physiological Action of Alkaloids

The commercial importance of alkaloids depends wholly on their therapeutical applications, and certain of them, such as quinine and morphine, are, and have long been, among the most commonly-used drugs. A good deal of attention has been given to the possibility of correlating the chemical constitution of alkaloids with their pharmacological action, but this subject is so full of difficulties on both the chemical and pharmacological sides, that comparatively little progress has been made. As an example of the difficulties encountered, even in a comparatively simple case, the investigations of Jowett and Pyman on the mydriatic effects of a whole series of tropeines may be quoted (p. 116) as a result of which they concluded that no definite generalisation as to the relation between the mydriatic action and chemical constitution of the tropeines can be made, which will explain the results they obtained.

In spite of these difficulties, many important and useful observations on this subject have been made, and such work as that done in the last few years by von Braun and others, leaves some hope that, with a better knowledge of the modes of action of drugs, further advance in this direction may be possible.

I. PYRROLE GROUP

A few simple derivatives of pyrrole, or of its reduction product pyrrolidine, occur in plants, and though these can hardly be regarded as alkaloids, they are briefly described here as representing possible precursors of the typical plant alkaloids.

Pictet and Court [1] have recorded the presence of pyrrolidine in tobacco and carrot leaves, in the former case along with 1-methylpyrrolidine, and in the second with DAUCINE, $C_{11}H_{18}N_2$, b.p. 240°–250,° $[\alpha]_D + 7.74°$, which does not give a pyrrole reaction. They also found a pyrrole base in carrot seeds and in parsley.

Proline Derivatives. Proline (pyrrolidine-2-carboxylic acid) does not occur in nature as such, but is one of the products of the hydrolysis of proteins. The simplest derivatives of proline of interest in connection with alkaloids are hygric acid (1-methylpyrrolidine-2-carboxylic acid) produced by the oxidation of hygrine, one of the secondary bases found in coca leaves (*see* p. 94), and 4-hydroxyproline, which, like proline itself, is a protein hydrolytic product. Closely related to both of these are 4-hydroxyhygric acid found in *Croton gubouga*, stachydrine occurring in *Stachys tuberifera*, and betonicine and turicine found in *Betonica officinalis*, *Stachys silvatica*, etc. The relationships of these various substances are shown by the following formulæ, in which the optically active carbon atoms are asterisked :
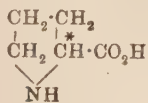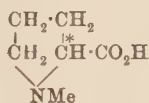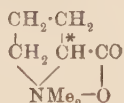
CH₂·CH₂ / CH₂ CH·CO₂H / NH	CH₂·CH₂ / CH₂ CH·CO₂H / NMe	CH₂·CH₂ / CH₂ CH·CO / NMe₂—O
Proline	*Hygric acid*	*Stachydrine*
HO·CH—CH₂ / CH₂ CH·CO₂H / NH	HO·CH—CH₂ / CH₂ CH·CO₂H / NMe	HO·CH—CH₂ / CH₂ CH·CO / NMe₂—O
4-Hydroxyproline	*4-Hydroxyhygric acid*	*Betonicine and Turicine*
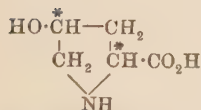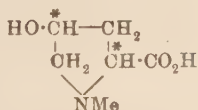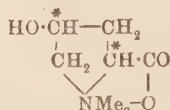
[1] *Bull. Soc. Chim.* 1907 [iv], **1**, 1001.

Stachydrine, $C_7H_{13}O_2N.H_2O$, was obtained from the roots of *Stachys tuberifera* (*S. Sieboldii*, Miq.) by von Planta and Schulze,[1] by Jahns from orange leaves,[2] by Steenbock from lucerne hay,[3] and has also been recorded from several other plants by Trier and collaborators.[4] It forms deliquescent crystals, m.p. 210° (*dry*), is readily soluble in alcohol or water, insoluble in ether or chloroform. It is stable to permanganate in acid solution, and gives a pyrrole reaction. The hydrochloride, B.HCl, forms large transparent prisms, m.p. 235°, and the hydrogen oxalate, $B.H_2C_2O_4$, needles, m.p. 105°–107°, insoluble in cold dry alcohol. The aurichloride, $B.HAuCl_4$, forms characteristic leaflets, m.p. 225°, becoming oily when warmed in water.

When heated with strong potash solution, stachydrine gives off dimethylamine.[5] It was first synthesised by Schulze and Trier [6] by treating ethyl hygrate methiodide with silver oxide, thus confirming the formula (*see* p. 15) previously suggested for it by the same authors. Stachydrine is usually described as optically inactive, but Yoshimura and Trier [7] obtained a lævorotatory form from *Galeopsis ochroleuca*, and Steenbock from lucerne hay, whilst Deleano [8] states that the base has $[\alpha]_D^{18°} - 26 \cdot 2°$ in water, but that this value is reduced to $- 9°$ by long contact with acids or alkalis and vanishes when the base is boiled with alkalis.

The supposed alkaloid chrysanthemine has been shown to be a mixture of stachydrine and choline.[9]

4-Hydroxyhygric Acid, $C_6H_{11}O_3N.H_2O$. This substance was isolated in 1919 by Goodson and Clewer from the bark of a South African plant, *Croton gubouga*,[10] S. Moore. It crystallises from water in truncated prisms, decomposes at 242°, has $[\alpha]_D - 84 \cdot 9°$, gives a strong pyrrole reaction and forms a well-crystallised copper salt. The constitution assigned to it (p. 15) was established by the fact

[1] *Berichte*, 1890, **23,** 1699 ; 1893, **26,** 939.

[2] *Ibid.* 1896, **29,** 2065.

[3] *J. biol. Chem.* 1918, **35,** 1.

[4] *Zeit. physiol. Chem.* 1912, **76,** 258 ; **77,** 290.

[5] Schulze and Trier, *Zeit. physiol. Chem.* 1909, **59,** 233 ; *cf.* Engeland, *Arch. Pharm.* 1909, **247,** 463.

[6] *Berichte*, 1909, **42,** 4654 ; *cf.* Trier, *Zeit. physiol. Chem.* 1910, **67,** 324.

[7] *Zeit. physiol. Chem.* 1912, **76,** 258 ; **77,** 290.

[8] *Bull. Soc. de Stiinte Bucuresti*, 1914, **23,** 39 ; *Chem. Soc. Abstr.* 1915, [i], 835.

[9] Marino-Zuco, *Chem. Soc. Abstr.* 1891, **60,** 333 ; 1892, **62,** 84 ; Yoshimura and Trier, *Zeit. physiol. Chem.* 1912, **77,** 290.

[10] *Trans. Chem. Soc.* 1919, **115,** 923.

that on treatment with methyl iodide it yields a mixture of betonicine and turicine (*see below*).

Betonicine and Turicine, $C_7H_{13}O_3N$. A mixture of these two betäines occurs in *Betonica officinalis* and *Stachys silvatica*, from which they were isolated by Küng and Trier.[1] Küng subsequently prepared them by methylating 4-hydroxyproline,[2] and they were also obtained by Goodson and Clewer[3] by methylating 4-hydroxy-hygric acid (*see above*). They are best separated by crystallising the free bases from alcohol, turicine being less soluble than its isomeride. Both give a pyrrole reaction.

Betonicine crystallises in four-sided, truncated pyramids, has a sweet taste, decomposes at 252° and has $[\alpha]_D - 35 \cdot 1°$ or $- 36 \cdot 6°$ in water. The hydrochloride, B.HCl, forms needles or prisms from dry alcohol, decomposes at 224°, has $[\alpha]_D - 24 \cdot 8°$ in water, and yields an aurichloride, $B.HAuCl_4$, which separates from water in clusters of yellow tablets, decomposing at 230°–232°. The platini-chloride, $B_2.H_2PtCl_6.2H_2O$, short prisms, decomposes at 226°.

Turicine forms flat prisms, containing one molecule of water, from alcohol, is sweet to the taste, decomposes at 260° (*dry*), has $[\alpha]_D + 36 \cdot 26°$ (monohydrated) in water. The hydrochloride, B.HCl, crystallises from dry alcohol in needles or six-sided tablets, decomposes at 224°, has $[\alpha]_D + 25 \cdot 7°$ in water, and yields an auri-chloride, clusters of yellow prisms, decomposing at 232°, and a platinichloride, m.p. 223°.

Though betonicine and turicine show optical rotation of opposite sign, they are believed not to be enantiomorphs. The formula assigned to them (p. 15) shows two asymmetric carbon atoms, and it is not yet known whether these are both active in both bases.

Pharmacological Action of Proline Derivatives. Most of these proline derivatives are slightly sweet to the taste, but are probably almost inactive physiologically : thus stachydrine taken by the mouth is largely excreted unchanged in the urine. According to Trier,[4] whilst hygric acid exhibits no toxic action, methyl hygrate, which is isomeric with stachydrine, and yields the latter on distillation, is a convulsant poison.

[1] *Zeit. physiol. Chem.* 1913, **85**, 209.
[2] *Ibid.* 1913, **85**, 217.
[3] *Trans. Chem. Soc.* 1919, **115**, 929.
[4] *Zeit. physiol. Chem.* 1910, **67**, 324.

Galegine. This base, isolated from *Galega officinalis* by Tanret, and regarded by this author as a derivative of pyrrolidine, has been shown by Barger and White, and independently by Späth and Prokopp, to be a derivative of guanidine, and is therefore dealt with in group 9, p. 343.

II. PYRIDINE GROUP

ALKALOID OF *RICINUS COMMUNIS*

Ricinine, $C_8H_8O_2N_2$, was first isolated by Tuson [1] from the seeds of the castor-oil plant, *Ricinus communis*, and has since been examined by Soave,[2] Schulze,[3] who obtained it from castor seedlings, and by Evans.[4] It crystallises in prisms, m.p. 201·5°, sublimes when gently heated, and dissolves readily in hot water or alcohol, less easily in ether or light petroleum. The solutions are neutral, and the alkaloid does not form salts, nor is it precipitated by the usual alkaloidal reagents with the exception of iodine or mercuric chloride. Ricinine, evaporated with nitric acid, leaves a yellow residue, which is turned purple by ammonia.

The first important contribution to knowledge of the constitution of ricinine was made by Maquenne and Philippe,[5] who showed that it was hydrolysed by alkalis to methyl alcohol and ricininic acid, $C_7H_6O_2N_2$, slender brilliant needles, m.p. 296°–298° (*decomp.*), which is very sparingly soluble in cold but moderately so in boiling water, and is hydrolysed by hydrochloric acid in closed vessels at 150°, yielding ammonia, carbon dioxide, and a base, $C_6H_7O_2N$, supposed to be *N*-methyl-3-hydroxy-1 : 4-dihydropyrid-4-one. On the strength of these observations, they assigned to ricinine and ricininic acid formulæ which were accepted until 1918, when Böttcher [6] drew attention to the fact that ricinine exhibited many of the reactions of glyoxaline, and showed in addition that, on heating with 50 per cent. sulphuric acid, an acid, m.p. 216°, is produced, which contains : NMe, gives the reactions of a pyridinecarboxylic acid, yields a pyrrole on distillation with lime, and forms the methyl-hydroxydihydropyridone referred to above on hydrolysis with

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[1] *Trans. Chem. Soc.* 1864, **17,** 195.

[2] *Abstr. Chem. Soc.* 1896 [i], 386.

[3] *Ibid.* 1898 [i], 42 ; 1905 [ii], 112.

[4] *Journ. Amer. Chem. Soc.* 1900, **22,** 39.

[5] *Compt. rend.* 1904, **138,** 506 ; **139,** 840.

[6] *Berichte,* 1918, **51,** 673.

2 2

hydrochloric acid at 150°. Winterstein, Keller and Weinhagen,[1] had in the meantime shown that the product formed by the action of 57 per cent. sulphuric acid on ricinine, has the formula, $C_7H_9O_2N$, and still contains the methoxyl group of ricinine. Späth and Tschelnitz [2] then re-examined the bases, $C_6H_7O_2N$ and $C_7H_9O_2N$, and showed that the former was N-methyl-4 (or 2)-hydroxy-1 : 2 (or 1 : 4)-dihydro-2 (or 4)-pyridone (the positions given in brackets representing an alternative possible constitution), and that the base, $C_7H_9O_2N$, was a methyl ether of this substance. Both bases were synthesised and shown to be identical with the two degradation products of ricinine. These authors, like Böttcher, at first proposed formulæ for the alkaloid which represented it as containing a glyoxaline ring, but these were withdrawn as a result of Späth and Koller's [3] synthesis of ricinidine. The latter is ricinine in which the methoxyl group is replaced by hydrogen in the following way. Ricinine is hydrolysed by potassium hydroxide to ricininic acid, the hydroxy-group of the latter replaced by chlorine by the action of phosphoryl chloride and the chloro-compound (which regenerates ricinine and ricininic acid if treated with methyl alcohol and sodium methoxide), reduced by hydrogen in presence of palladinised barium sulphate to RICINIDINE, $C_7H_6ON_2$, m.p. 140°, b.p. 243°/18 mm. The latter, on hydrolysis, yields first an amide, $C_7H_8O_2N_2$, and then a carboxylic acid, $C_7H_9O_3N$, obviously by the hydrolysis of a .CN group, so that the acid appeared to be one of the three possible N-methyl-2-pyridone-carboxylic acids, all of which were synthesised. The required acid was obtained by the action of methyl iodide on the di-silver salt of 2-hydroxypyridine-3-carboxylic acid and hydrolysis of the product to N-methyl-2-pyridone-3-carboxylic acid, which proved to be identical with the one obtained from ricinidine. This acid was then converted into the amide by the use of thionyl chloride and ammonia, and the amide, by the action of thionyl or phosphoryl chloride into the corresponding cyano-compound, which proved to be ricinidine. The salient steps in the degradation of ricinine and the synthesis of ricinidine may be represented as on next page.

While this volume was in the press, Späth and Koller completed the synthesis of ricinine, and so established the validity of the formula given.[3]

[1] *Arch. Pharm.* 1917, **255**, 513.
[2] *Monatshefte*, 1921, **42**, 251.
[3] *Berichte*, 1923, **56**, 880 ; synthesis of ricinine. *ibid.* p. 2454.

$$C.OCH_3 \quad\rightarrow\quad C.OH \quad\rightarrow\quad CH$$

CH C.CN   CH C.CN   CH C.CN

CH CO   CH CO   CH CO

N.CH$_3$ N.CH$_3$ N.CH$_3$

Ricinine   *Ricininic acid*   *Ricinidine*

CH   CH   CH

CH C.COOH   CH C.COOH   CH C.CONH$_2$

CH C.OH   CH CO   CH CO

N   N.CH$_3$ N.CH$_3$

2-Hydroxypyridine-   *N-methyl-2-pyridone-*   *N-methyl-2-pyridone-*
3-carboxylic acid   *3-carboxylic acid*   *3-carboxylic acid amide*]
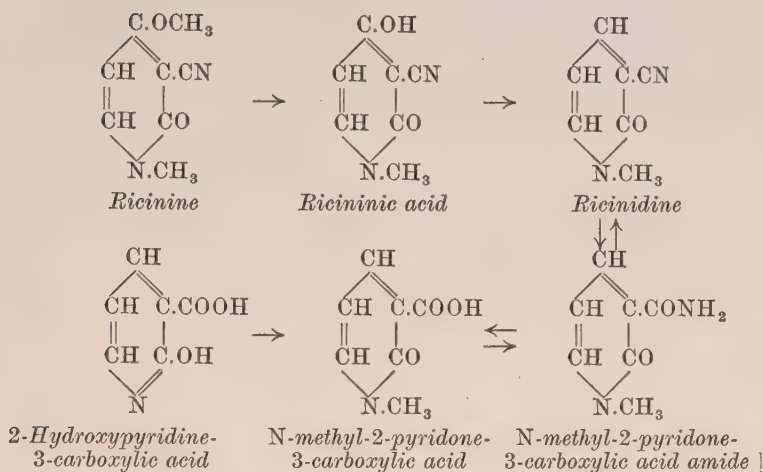
Ricinine is not markedly toxic, the poisonous character of castor-oil seeds being due to a much more complex substance, ricin, the activity of which can be destroyed by heat.

ALKALOID OF *FŒNUGREC*

Trigonelline, $C_7H_7O_2N.H_2O$. This alkaloid was isolated by Jahns [1] from the seeds of *Trigonella Fœnum-græcum*, a leguminous annual cultivated in India and Egypt for the sake of its seeds (fœnugrec), which are used to a small extent in the preparation of curries, but chiefly for the manufacture of cattle-foods. Trigonelline has also been detected in a number of other plants, *e.g.*, by Schulze and Frankfort [2] in the seeds of *Pisum sativum*, and by Thoms in *Strophanthus hispidus* and *Strophanthus Kombé*.[3] According to Gorter [4] it is present in coffee, whence it was isolated under the name " caffearine " by Palladino.[5]

Jahns obtained the alkaloid by exhausting ground fœnugrec seeds with 70 per cent. alcohol. The concentrated extract was freed from colouring matter by lead acetate, and from soluble proteins by evaporation to a syrup and addition of strong alcohol. An aqueous solution of potassium bismuth iodide was then added

[1] *Berichte*, 1885, **18**, 2518.
[2] *Ibid.*, 1894, **27**, 769.
[3] *Ibid.* 1898, **31**, 271, 404.
[4] *Annalen*, 1910, **372**, 237 ; *cf.* Polstorff, *Chem. Soc. Abstr.* 1910, [ii], 234.
[5] *Chem. Soc. Abstr.* 1894, [i], 214 ; 1895, [i], 629 ; *cf.* Graf, *ibid.* 1904, [i], 915.

and the mixture set aside for some weeks. The precipitate was treated with a solution of caustic soda and the filtrate neutralised by sulphuric acid.   Sufficient mercuric chloride was added to form sodium-mercuric iodide, which under these conditions precipitates the small amount of choline present.   Trigonelline mercuric iodide crystallises from the filtrate on addition of an acid, and from this the pure alkaloid may be regenerated by any of the ordinary methods.[1]

Trigonelline crystallises from alcohol in hygroscopic prisms containing one molecule of water, m.p. 130° or 218° (dry, decomp.).   It is very soluble in water, less so in cold alcohol, and slightly so in ether or chloroform.

The salts crystallise well, the hydrochloride, B.HCl, in anhydrous leaflets, and the platinichloride in yellow prisms. The alkaloid forms several aurichlorides : the normal salt, $B.HCl.AuCl_3$, is precipitated when excess of gold chloride is added to trigonelline hydrochloride. It can be recrystallised from dilute hydrochloric acid and then forms flattened prisms, m.p. 198°. Crystallised from water or very dilute hydrochloric acid, fine needles, $B_4.3HAuCl_4$, m.p. 186°, are obtained.

When trigonelline is heated in closed tubes with baryta water at 120° it gives rise to methylamine, whilst hydrochloric acid at 260° furnishes methyl chloride and nicotinic acid.[2]   This reaction, which may be represented by the equation

$$C_7H_7O_2N \quad + HCl \qquad = C_6H_5O_2N \qquad + CH_3Cl$$
Trigonelline   *Pyridine-3-carboxylic acid*
                              (nicotinic acid)
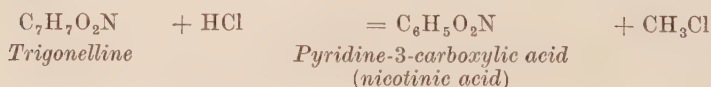
indicates that the alkaloid is a betäine of nicotinic acid.
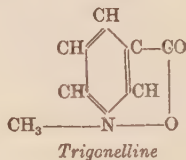
Trigonelline

Hantzsch [3] prepared this betäine in 1886 by hydrolysing nicotinic acid methiodide with silver hydroxide, and Jahns [4] subsequently identified trigonelline with Hantzsch's synthetic base.

Trigonelline appears to exert no pharmacological action, and it

[1] *Cf.* Schulze, *Zeit. physiol. Chem.* 1909, **60,** 155, and Gorter (*loc. cit.*).
[2] Jahns, *Berichte,* 1887, **20,** 2840.
[3] *Berichte,* 1886, **19,** 31.
[4] *Ibid.* 1887, **20,** 2840.

is interesting to note that when nicotinic acid is administered to dogs it appears in the urine as trigonelline.[1]

ALKALOIDS OF *ARECA* NUT (*Areca Catechu*)

The areca or betel-nut palm (*Areca Catechu*) is indigenous to the Sunda Islands, but is now widely cultivated in tropical countries of the Far East, where the seeds are employed mixed with lime and betel pepper leaves (*Piper Betle* L.) as a masticatory. In China and India ground areca nut is used as a vermifuge, and it is also employed in this way in Europe in veterinary medicine.

The seeds were first examined by Bombelon [2] and later by Jahns,[3] who isolated, in addition to choline, the four alkaloids arecoline, arecaidine, arecaine and guvacine, of which arecaine is now known to be identical with arecaidine. Emde [4] added to these arecolidine, and K. Hess,[5] guvacoline.

Jahns prepared his alkaloids by digesting the ground seeds three times with water containing 2 grm. of sulphuric acid per kilogram of seeds, and precipitating the concentrated extract with potassium bismuth iodide solution, avoiding excess; from the washed precipitate the alkaloids were regenerated by boiling with water containing barium carbonate. The aqueous solution so obtained on concentration and addition of barium hydroxide gave up to ether, arecoline, which can be purified through the hydrobromide. The residual solution was neutralised with sulphuric acid and treated successively with silver sulphate, barium hydroxide, and carbon dioxide, and the final filtrate evaporated to dryness and extracted with dry alcohol or chloroform, which left arecaine undissolved, arecaidine and guvacine passing into solution. Arecaine was purified by repeated crystallisation from 60 per cent. alcohol, and finally by treating the crude product with methyl alcohol and hydrogen chloride, which converted arecaidine into arecoline, but left arecaine unaffected. Guvacine sometimes replaces arecaine in part in the seeds, and is separated from arecaine and arecaidine by taking advantage of its smaller solubility in water or dilute alcohol. Like arecaine, it is unaffected by treatment with methyl alcohol

[1] Ackermann, *Zeit. Biol.* 1912, **59**, 17; *cf.* Kohlrausch, *ibid.* 1911, **57**, 273.

[2] *Pharm. Zeit.* 1886, p. 146.

[3] *Berichte*, 1888, **21**, 3404; 1890, **23**, 2972; 1891, **24**, 2615; *Arch. Pharm*, 1891, **229**, 669.

[4] *Apoth. Zeit.* 1915, **30**, 240 (*Chem. Soc. Abstr.* 1915, [i], 981).

[5] *Berichte*, 1918, **51**, 1004.

and hydrogen chloride, and may in this way be purified from the last traces of arecaidine. Arecoline is present to the extent of 0·07 to 0·1, and arecaine to about 0·1 per cent. Arecaidine and guvacine occur in smaller quantities, whilst guvacoline and arecolidine are found only in minute proportions in the mother liquors.

Much of this is now known to be inaccurate since arecaine has been shown to be identical with arecaidine, and guvacine is known to undergo esterification with methyl alcohol and hydrogen chloride, and any one using this process must vary it accordingly.

The alkaloids known to occur in areca nut, with their formulæ, are as follows :

Guvacine, $C_6H_9O_2N$.   *Guvacoline*, $C_7H_{11}O_2N$ (Guvacine methyl ester).

Arecaidine, $C_7H_{11}O_2N$.   *Arecoline*, $C_8H_{13}O_2N$ (Arecaidine methyl ester).

Arecolidine, $C_8H_{13}O_2N$.   *Arecaine* = Arecaidine.

Guvacine, $C_6H_9O_2N$.   This, the simplest alkaloid of the areca-nut series, was first isolated by Jahns. It forms small lustrous prisms, m.p. 271°–272°(J.),[1] m.p. 293°–295° (W. and W.)[2], is neutral to litmus, optically inactive and moderately soluble in water or dilute alcohol, but almost insoluble in other solvents. The hydro-chloride, B.HCl, crystallises in prisms, m.p. 312° (W. and W.),[2] 316° (F.),[3] sparingly soluble in dilute hydrochloric acid ; the platini-chloride, $B_2.H_2PtCl_6,4H_2O$, forms hexagonal prisms from water, m.p. 211° (J.),[1] 233° (W. and W.),[2] 220°–221° (F.)[3]; the auri-chloride, B.HAuCl₄, broad flattened prisms, m.p. 194°–195° (J.),[1] 195°–197° (W. and W.),[2] 197°–199° (F.).[3] The base and its salts decompose on melting.

Guvacine reacts like a secondary amine furnishing a nitroso-compound, m.p. 167°–168° (J.), and an acetyl derivative, m.p. 189°–190°, whilst on distillation with zinc dust it yields β-picoline (3-methylpyridine). On treatment with sodium methoxide and potassium methyl sulphate, Jahns obtained arecaine and a second substance isomeric with this, and since he was unable to prove the presence of a carboxyl group, assigned to guvacine and arecaine formulæ different in type from those attributed to arecaidine and

[1] Jahns, *Berichte*, 1891, **24**, 2615.
[2] Winterstein and Weinhagen, *Zeit. physiol. Chem.* 1918, **104**, 48.
[3] Freudenberg, *Berichte*, 1918, **51**, 1669.

arecoline.[1]   Though Trier [2] in 1913 first suggested for guvacine a formula containing a carboxyl group (Δ^1-tetrahydropyridine-3-carboxylic acid), it was not until 1918, when Freudenberg called attention to the close agreement between the melting points of guvacine and its derivatives with those of Δ^3-tetrahydropyridine-3-carboxylic acid (synthesised by Wohl and Losanitsch [3] five years previously) and its derivatives, that the many anomalies of guvacine as formulated by Jahns were explained.   Freudenberg [4] subsequently demonstrated the identity of guvacine with Wohl and Losanitsch's acid, and showed that guvacine, contrary to Jahns' experience, does yield a methyl ester, subsequently accepted by K. Hess as identical with guvacoline,[5] which, on treatment with methyl iodide, gives a mixture of arecoline methiodide and hydriodide of which the latter yields arecaidine on hydrolysis.   As arecaidine and arecoline had been synthesised already and shown to be respectively 1-methyl-Δ^3-tetrahydropyridine-3-carboxylic acid and the methyl ester of this acid, there can be little doubt that guvacine is the corresponding secondary base, viz., Δ^3-tetrahydropyridine-3-carboxylic acid.   This observation also indicates that arecaine, obtained by Jahns,[6] and by Hess and Leibbrandt [5] by the methylation of guvacine is identical with arecaidine.

*iso*Guvacine.   In his description of the isolation of guvacine, Jahns mentioned that he obtained a small fraction of another crystalline alkaloid of lower melting-point.   This fraction Trier [7] named *iso*guvacine, and Winterstein and Weinhagen [8] have given a brief description of it and some of its salts.   The base has m.p. 220°, is faintly acid to litmus, optically inactive and yields crystalline salts :   hydrochloride, m.p. 231°, platinichloride, m.p. 235°, and aurichloride, m.p. 198°–200°. It yields a dimethyl derivative, the platinichloride of which has m.p. 252°.   These melting-points suggest that the substance is mainly arecaidine, but the authors, on the ground that it yields on distillation with zinc dust a substance giving the pyrrole reaction, suggest that it is a simple pyrrole derivative isomeric with guvacine.

[1] *Arch. Pharm.* 1891, **229,** 669.
[2] *Zeit. physiol. Chem.* 1913, **85,** 372.
[3] *Berichte,* 1907, **40,** 4701.
[4] *Ibid.* 1918, **51,** 976, 1669.
[5] *Ibid.* 1918, **51,** 806 ; 1919, **52,** 206.
[6] *Arch. Pharm.* 1891, 229, 669 ; *cf.* Trier, *Zeit. physiol. Chem,* 1913, 85, 372.
[7] *Zeit. physiol. Chem.* 1913, **85,** 391.
[8] *Ibid.* 1918, **104,** 48.

Guvacoline, $C_7H_{11}O_2N$ (*guvacine methyl ester*).   K. Hess[1] assigns this name and constitution to an alkaloid obtained from areca nut, and which yields a hydrobromide, short prisms, m.p. 144°–145°, that he identified with guvacine methyl ester hydrobromide, by its hydrolysis to guvacine and by comparison with the methyl ester hydrobromide prepared from guvacine.   This alkaloid is, therefore, identical [2] with the guvacine methyl ester, b.p. 114°/13 mm. prepared by Freudenberg,[3] which yields a hydrochloride, leaflets, m.p. 121°–122°, a platinichloride, golden leaflets, m.p. 211°, and on methylation arecoline methiodide and hydriodide (*see* p. 25).

Arecaidine (Arecaine), $C_7H_{11}O_2N \cdot H_2O$.   This alkaloid forms colourless four-or six-sided tablets, m.p. 222°–223° (J.),[4] 232° (H. and L.),[5] is readily soluble in water, but practically insoluble in all organic solvents, including dry alcohol.   The hydrochloride, $B \cdot HCl$, forms slender colourless needles, m.p. 257°–258° (H. and L.),[5] sparingly soluble in cold dry alcohol; the platinichloride, $B_2 \cdot H_2PtCl_6$, crystallises in octahedra, m.p. 225°–226° [6] and the aurichloride, $B \cdot HAuCl_4$, in prisms, m.p. 197°–198° from hot dilute hydrochloric acid.

Constitution.   Since arecaidine furnishes a methyl ester (arecoline), it must contain a carboxyl group, and its formula may be written, $C_6H_{10}(COOH)N$, which is that of a methyltetrahydropyridine-carboxylic acid.   This consideration led Jahns to attempt the synthesis of arecaidine by methylating the potassium salt of nicotinic acid, and reducing, and incidentally hydrolysing, the methyl ester methochloride obtained, with the result that a base identical with arecaidine was obtained, along with some dihydroarecaidine.   From the fact that arecaidine, whether isolated from areca nuts or synthesised as already described, is optically inactive and cannot be resolved into two optical isomerides, Meyer [7] concluded that it is N-methyl-Δ^3-tetrahydronicotinic acid, and this has been confirmed by Wohl and Johnson's [8] complete synthesis of the alkaloid from acroleïn as a starting-point (*see* under arecoline, p. 27).

[1] *Berichte*, 1918, **51**, 1004.
[2] Hess and Leibbrandt, *ibid.* 1919, **52**, 206.
[3] *Ibid.* pp. 976, 1668.
[4] Jahns, *Arch. Pharm.* 1891, **229**, 669.
[5] K. Hess and F. Leibbrandt, *Berichte*, 1919, **52**, 206.
[6] Wohl and Johnson, *Berichte*, 1907, **40**, 4712.
[7] *Monatshefte*, 1902, **23**, 22.
[8] *Berichte*, 1907, **40**, 4712.

| Potassium nicotinate | Methyl nicotinate methiodide | Arecaidine (Jahns and Meyer) |
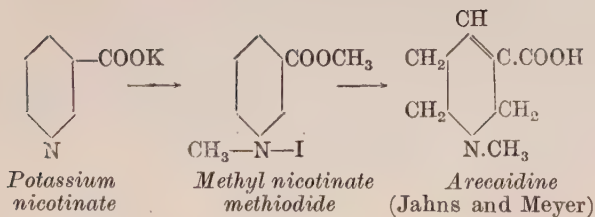
K. Hess and F. Leibbrandt [1] have also prepared arecaidine by brominating methyl N-methylhexahydronicotinate, removing the elements of hydrogen bromide from the resulting methyl N-methyl-3-bromohexahydronicotinate and hydrolysing the arecoline so formed.

The identity of arecaine with arecaidine and the formation of the latter from guvacine which have been referred to already, indicate that it is N-methylguvacine (p. 25).

Arecoline, $C_8H_{13}O_2N$, is a colourless, odourless, strongly alkaline liquid, b.p. 220°, volatile in steam, miscible with water and most organic solvents in all proportions, but is extracted from water by ether in presence of dissolved salts. It furnishes crystalline, but usually deliquescent salts; the hydrobromide, B.HBr, forms slender prisms, m.p. 167°–168° from hot alcohol; the aurichloride, B.HAuCl$_4$, is an oil, but the platinichloride, [B.HCl]$_2$.PtCl$_4$, m.p. 176°, crystallises from water in orange-red rhombs. The methiodide forms glancing prisms, m.p. 173°–174°.

When heated with hydrochloric or hydriodic acid, or with alkalis, arecoline yields arecaidine and methyl chloride, iodide or hydroxide, respectively. Conversely, on esterification with methyl alcohol, arecaidine yields arecoline. The ethyl ester of arecaidine has also been prepared; it is known as *homoarecoline*, closely resembles arecoline, and, like it, is poisonous.

The preparation of arecaidine from potassium nicotinate has been described already. A complete synthesis of arecaidine, and consequently of arecoline, has been effected by Wohl and Johnson. [2] Acroleïn (I) was converted into β-chloropropaldehyde acetal (II) by the action of alcohol and hydrogen chloride, and this was condensed with methylamine, giving β-methyliminodipropaldehyde tetra-ethylacetal (III). This on treatment with cold strong hydrochloric acid, gave N-methyl-Δ^3-tetrahydropyridine-3-aldehyde (IV), from the oxime of which thionyl chloride abstracted the elements

[1] *Berichte*, 1918, **51**, 812.   [2] *Ibid.* 1907, **40**, 4712.

of water, yielding 3-cyano-N-methyl-Δ^3-tetrahydropyridine hydrochloride, and this on hydrolysis gave arecaidine, from which arecoline may be prepared by esterification with methyl alcohol in the usual way.

HC:O   HC$\Big\langle^{OEt}_{OEt}$ HC$\Big\langle^{OEt}_{OEt}$ $^{OEt}_{OEt}\Big\rangle$CH

CH   CH$_2$ CH$_2$ CH$_2$ CH$_2$—CH $=$ C.CHO

CH$_2$ CH$_2$Cl   CH$_2$——NMe——CH$_2$ CH$_2$—NMe —CH$_2$ →

(I)   (II)   (III)   (IV)

CH$_2$ CH
CH$_2\Big\langle$ $\Big\rangle$C.COOH → CH$_2\Big\langle$ $\Big\rangle$C.COOMe
NMe CH$_2$ HCl.NMe CH$_2$

Arecaidine   *Arecoline hydrochloride*
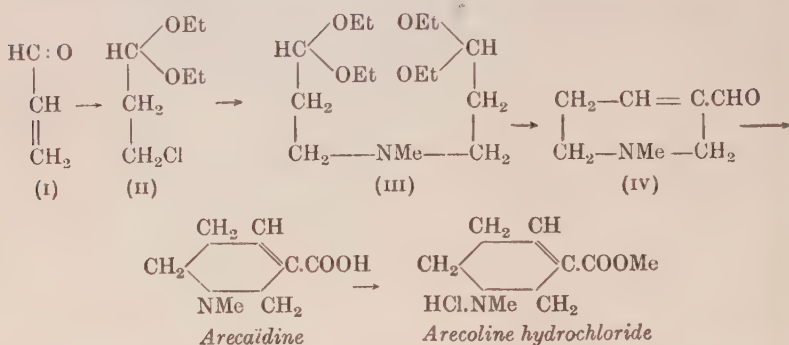
Arecolidine, $C_8H_{13}O_2N$. This alkaloid was obtained by Emde [1] in minute quantity from the mother liquors available from the technical preparation of its isomeride, arecoline. It is a weak base, crystallises from dry ether in glassy needles, m.p. 105°, but after sublimation, has m.p. 110°, and is very hygroscopic. The hydrochloride, B.HCl.H$_2$O, hydrobromide, m.p. 268°–271° (*decomp.*), aurichloride, yellow leaflets, m.p. 219°–220° (*decomp.*), and platinichloride, thick, dark orange needles, m.p. 222°–223° (*decomp.*) were prepared. The base gives a methiodide, prisms, m.p. 264° (*decomp.*), and methylarecolidine, $C_9H_{15}O_2N$, derived from this yields a normal aurichloride, m.p. 252°. Arecolidine is regarded by Emde as 3 : 4-dimethoxy-1-methyl-1 : 2-dihydropyridine, but the evidence for this is slight and indirect.

Pharmacological Action of the Areca Nut Alkaloids. Of these alkaloids arecoline alone exhibits markedly toxic properties. According to Meier [2] it belongs to the nicotine-pilocarpine group and acts on the central and peripheral nervous system producing paralysis, which may be preceded by convulsions. With nicotine the central and with pilocarpine the peripheral action is the more marked, whilst both are about equal in arecoline. Arecoline hydrobromide is recognised in several Continental pharmacopœias, being used internally in small doses as a sialogogue and diaphoretic, and as an anthelmintic. It has also been employed like physostigmine to produce myosis.

[1] *Apoth. Zeit.* 1915, **30**, 240 ; *Chem. Soc. Abstr.* 1915, [i], 981.
[2] *Bio. chem. Zeit.* 1907, **2**, 415 ; *Chem. Soc. Abstr.* 1907, [ii], 118.

ALKALOIDS OF HEMLOCK

The common hemlock, *Conium maculatum*, contains a series of five alkaloids. Power and Tutin have found a similar mixture of alkaloids in fool's parsley,[1] and a volatile alkaloid resembling coniine is stated to occur in certain aroids.[2] The toxic properties of hemlock juice have been known from very early times ; thus it was the chief ingredient in the poison administered to criminals by the Greeks. The value of hemlock as a medicine was recognised by the Anglo-Saxons, but its modern employment is due to Storck in 1760, and Harley in 1867, although it has to some extent fallen into disrepute owing to the uncertainty of action shown by galenical preparations made from it.[3] The leaves and the unripe fruits are the parts of the plant used in medicine. The following are the names and formulæ of the hemlock alkaloids :

> *Coniine*, $C_8H_{17}N$ (*d*- and *l*-forms).
> N-*Methylconiine*, $C_8H_{16}N.CH_3$ (*d*- and *l*-forms).
> γ-*Coniceine*, $C_8H_{15}N$.
> *Conhydrine*, $C_8H_{17}ON$.
> ψ-*Conhydrine*, $C_8H_{17}ON$.

Estimation of the Total Alkaloids of Hemlock. The following method was prescribed in the United States Pharmacopœia (8th Revision) for the estimation of the total alkaloids in hemlock fruits.

Ten grammes of the fruits in No. 60 powder are allowed to stand with occasional shaking during four hours with 100 c.c. of a mixture of ether 98 parts, alcohol 8 parts, and ammonia water (sp. gr. 0·958 at 25°) 3 parts. Fifty cubic centimetres of the clear liquid (= 5 grm. of the fruits) are acidified with N-sulphuric acid and the ether evaporated ; 15 c.c. of alcohol are then added, and the mixture set aside during two hours to allow ammonium sulphate to deposit. The liquid is filtered off, the filter and residue washed with a little alcohol and the washings added to the filtrate, to which sodium carbonate solution is added until it remains faintly acid. The filtrate is then evaporated on the water-bath to 3 c.c., its own volume of water added, and 2 drops of N-sulphuric acid. It is then washed twice, using 15 c.c. of ether each time, transferred to a separator, sodium carbonate solution added until the liquid is slightly alkaline, and the alkaloids extracted by shaking successively with 15, 15, and

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[1] *Journ. Amer. Chem. Soc.* 1905, **27**, 1461.
[2] Hébert and Heim, *Bull. Soc. Chim.* 1898 [iii], **17**, 664.
[3] *Pharmacographia,* London, 1879, 299.

10 c.c. of ether.   The combined ether solutions are run into a tared beaker, 5 per cent. hydrochloric acid added drop by drop until the reaction is acid, and the ether evaporated on the water-bath.   The residue is evaporated twice with 3 c.c. of alcohol to remove excess of acid and finally dried at a temperature not exceeding 60° and weighed.   This weight multiplied by 0.777×20 gives the percentage of total alkaloids in the fruits.   The United States Pharmacopœia (VIII) required that it should not be less than 0.5 per cent.

An alternative method of estimating the alkaloidal constituents of hemlock or its galenical preparations is that devised by Cripps, and improved by Farr and Wright.[1]   Five grammes of the finely powdered fruits are mixed with sand and exhausted by percolation with a mixture of 95 per cent. alcohol 25 c.c., chloroform 15 c.c., and chloroform saturated with hydrogen chloride 10 c.c.   The extract is shaken twice with 25 c.c. of distilled water, the latter clarified by shaking once with a few cubic centimetres of chloroform, made alkaline by addition of caustic soda solution, and the liberated bases extracted by agitation with chloroform, the latter being then run into excess of a saturated solution of hydrogen chloride in chloroform.   The solvent is distilled off, and the residue of hydrochlorides dried at 90° in a current of air and weighed.

The alkaloidal values (expressed as total hydrochlorides) of the various parts of the plant have been recorded by Farr and Wright [2] as follows : stem 0.01 to 0.06, leaves 0.03 to 0.18, flowers 0.086 to 0.236, green fruit 0.725 to 0.975 per cent.   The fruit, which is the part mostly used in medicine, appears to contain most alkaloid when from three-fourths to full grown.   An examination of commercial samples of the drug as imported into the United Kingdom in 1904,[3] showed that these contained percentages of total alkaloids varying from 0.096 to 0.832 ; English fruits collected by the same authors yielded 1.05 to 3.57 per cent.

Coniine, $C_8H_{17}N$.   This alkaloid was first isolated by Giesecke in 1827.   For many years the formula assigned to it was $C_8H_{15}N$, and the present formula is due to Hofmann.[4]

Coniine is obtained from crushed hemlock fruits by allowing these to stand with dilute sodium carbonate solution and steam-distilling the mixture.   The distillate, containing the mixed volatile

[1] *Pharm. Journ.* 1887–8 [iii], **18,** 13, 511 ; 1891 [iii], **21,** 857, 936.
[2] *Ibid.* 1895–6 [iv], **1,** 89.
[3] *Loc. cit.* 1904 [iv], **18,** 185.
[4] *Berichte,* 1881, **14,** 705.

alkaloids with ammonia, is neutralised with hydrochloric acid, evaporated to dryness, and the residue extracted with dry alcohol, which dissolves the alkaloidal hydrochlorides and some ammonium chloride. The latter is removed by adding dry ether to the alcoholic solution. The residue left on evaporation of the alcohol-ether solution is dissolved in cold water, ether added, and the bases liberated by the addition of soda, and the whole shaken. The ethereal solution is dried with potassium carbonate and the ether distilled off at a low temperature, when the mixed alkaloids remain as an oily liquid. These may be separated to a certain extent by fractional distillation in a current of hydrogen, conhydrine being left as a residue if the temperature does not exceed 190° ; the coniine and γ-coniceine passing over together in the first fractions. For the separation of coniine from coniceine, Wolffenstein [1] recommends the conversion of the mixed bases into hydrochlorides. These are dried and extracted with acetone, which dissolves conicëine hydrochloride, leaving the coniine salt, from which the base may then be regenerated. For final purification the coniine should be converted into the *d*-hydrogen tartrate by dissolving 135·5 grm. of the product in a solution of 160 grm. of *d*-tartaric acid in 450 grm. of water, kept cool. It is sometimes necessary to start crystallisation by adding a crystal of the desired salt. von Braun distils the crude mixed alkaloids until the temperature rises to 190°, benzoylates the distillate, extracts the tertiary bases by shaking an ethereal solution with dilute acid, pours the concentrated ethereal solution into light petroleum to precipitate most of the benzoyl-δ-aminobutyl propyl ketone formed by the action of benzoyl chloride on coniceine, distils the solvent from the filtrate and collects from the residue the fraction boiling at 200°–210° under 16 mm. pressure, which is nearly pure benzoylconiine. From this a mixture of *d*- and *l*-coniines is obtained by hydrolysis, the former predominating. [2]

d-Coniine when pure is a colourless, strongly alkaline liquid, having a peculiar penetrating odour and a burning taste ; it boils at 166°–167°, has D^0 0·8626 and D^{19} 0·8438, refractive index n_D 1·4505, and is dextrorotatory, $[\alpha]_D^{19°} + 15·7°$. When cooled to $-2°$ it solidifies to a soft crystalline mass.

Coniine is slightly soluble (1 in 90) in cold water, but less so in hot water, so that a clear cold solution becomes turbid when warmed. On the other hand, the base dissolves about 25 per cent. of water at

[1] *Berichte*, 1894, **27**, 2615.
[2] *Ibid.* 1905, **38**, 3108.

atmospheric temperature. It mixes with alcohol in all proportions, is readily soluble in ether, but much less so in chloroform. Coniine slowly oxidises in the air. The ordinary salts crystallise well and are soluble in water or alcohol. The hydrochloride, $B.HCl$, crystallises from water in large rhombs, m.p. 220° ; the hydrobromide, needles, m.p. 211°, and the d-acid tartrate, $B.C_4H_6O_6.2H_2O$, in large rhombic crystals, m.p. 54°. The platinichloride, $(B.HCl)_2.PtCl_4.H_2O$, separates from concentrated solution as an oil, which solidifies to a mass of orange-yellow crystals, m.p. 175° (*dry*). The aurichloride, $B.HAuCl_4$, crystallises on standing, m.p. 77°. The picrate forms small yellow needles, m.p. 75°, from hot water. Coniine dissolves in carbon disulphide, forming a complex thiocarbamate.[1] It gives no coloration with sulphuric or nitric acid. The precipitate afforded by potassium cadmium iodide solution is crystalline, m.p. 118°, whilst that given by nicotine with this reagent is amorphous. Sodium nitroprusside gives a deep red colour, which disappears on warming, but reappears on cooling, and is changed to blue or violet by aldehydes.[2]

l-**Coniine** has $[\alpha]_D^{21°} - 15°$, and in other respects resembles its *d*-isomeride, but the salts have slightly different melting points ; the platinichloride has m.p. 160° (175° L and F), the aurichloride m.p. 59°, and the picrate m.p. 74°.[3]

Constitution. When coniine hydrochloride is distilled with zinc dust a new base, conyrine, is produced which Ladenburg proved to be 2-propylpyridine. At a later date the same author showed that the distillate also contained a stereoisomeride of *d*-coniine, which he called *iso*coniine.[4] Wolffenstein [5] regards *iso*coniine as a mixture of *d*-coniine with *dl*-coniine, but according to Ladenburg this is impossible, since *iso*coniine has a higher rotation than *d*-coniine, He finds that on reducing methylpicolylalkine, $C_5H_4N.CH_2.CHOH.CH_3$, with phosphorus and hydriodic acid, treating the product with zinc dust and water, and reducing the propylpyridine formed with sodium and alcohol, the propylpiperidine so produced has, after deracemisation with tartaric acid, $[\alpha]_D^{18.5°} + 17.85°$, and is

[1] Melzer, *Arch. Pharm.* 1898, **236**, 701.

[2] Gabutti, *Chem. Soc. Abstr.* 1906, [ii], 711. For a useful account of the colour reactions of coniine and the related alkaloids, see Dilling, *Pharm. Journ.* 1909 [iv], **29**, 34, 70, 102.

[3] Ahrens, *Berichte*, 1902, **35**, 1330. *Cf.* Löffler and Friedrich, *ibid.*, 1909, **42**, 107.

[4] *Ibid.* 1884, **17**, 772, 1121, 1676 ; 1885, **18**, 1587 ; 1893, **26**, 854 ; 1894, **27**, 853, 859 ; 1896, **29**, 2706.

[5] *Ibid.* 1894, **27**, 2615 ; 1896, **29**, 1956.

identical with *iso*coniine,[1] but K. Hess and W. Weltzien have stated recently that if care is taken to avoid the intermediate formation of 2-allylpyridine, *dl*-coniine only is formed, and from this by deracemisation only *d*-coniine having $[\alpha]_D^{17°} + 14 \cdot 96°$ is obtained.[2] A similar explanation had already been suggested by Löffler,[3] but was not accepted by Ladenburg.[1] Hofmann reduced conyrine by means of phosphorus and hydriodic acid to *dl*-coniine.[4] These and other reactions indicate that coniine is 2-propylpiperidine.

A number of syntheses of coniine have been effected, of which the first was that of Ladenburg, who prepared the alkaloid by reducing 2-*iso*allylpyridine with sodium in alcohol and deracemising the product and thus accomplished the first synthesis of a naturally occurring alkaloid. This method yields a coniine of high rotation (*iso*coniine ; *see above*), which is convertible into *d*-coniine of normal rotation by long heating in sealed tubes at 290° C.[5]

More recently Lautenschläger and Onsager [6] obtained *dl*-coniine (*d*) as a by-product in the conversion of pyridine-2-aldehyde (*a*) into 2 - hydroxypropylpiperidine (*c*) by the use of ethylmagnesium bromide and reduction of the 2-hydroxypropylpyridine (*b*) first formed : (*a*) $C_5H_4N.CHO + C_2H_5MgBr \rightarrow C_5H_4N.CH$ $(C_2H_5).OMgBr \rightarrow$ (*b*) $C_5H_4N.CHOH.C_2H_5 \rightarrow$ (*c*) $C_5H_{10}N.CHOH.$ $C_2H_5 \rightarrow$ (*d*) $C_5H_{10}N.CH_2.C_2H_5$.

The preparation of *l*-coniine by the reduction of β-conicëine (*l*-allylpiperidine *see* p. 37) by Löffler and Friedrich [7] is interesting as affording a means of passing from conhydrine (p. 34) to *l*-coniine. Hess and Eichel [8] have also shown that pelletierine, the principal alkaloid of pomegranate bark (p. 41) is the aldehyde (β-2-piperidylpropaldehyde) corresponding to coniine, and yields *dl*-coniine when its hydrazone is heated with sodium ethoxide in alcohol at 156°–170°. According to these authors *d*-coniine is rendered almost optically inactive when heated with barium hydroxide and alcohol at 180°– 230°.

***N*-Methyl-*d*-coniine,** $C_8H_{16}N.CH_3$. This alkaloid is stated to

[1] *Berichte*, 1906, **39**, 2486 ; 1907, **40**, 3734.
[2] *Ibid.* 1920, **53**B, 139.
[3] *Habilitationsschrift*, 1906.
[4] *Berichte*, 1884, **17**, 831.
[5] *Ibid.* 1886, **19**, 439, 2582 ; 1889, **22**, 1403 ; 1906, **39**, 2486 ; 1907, **40**, 3734.
[6] *Ibid.* 1918, **51**, 602.
[7] *Ibid.* 1909, **42**, 948.
[8] *Ibid.* 1917, **50**, 1192.

occur in hemlock in small quantities.[1] According to Wolffenstein [2] it remains with γ-coniceïne when the latter is separated from crude coniine by the fractional crystallisation of the acid tartrates. von Braun obtains the methylconiines from crude coniine by benzoylating the latter, dissolving the product in ether, and extracting the tertiary bases in which d-methylconiine predominates, with dilute acid.[3] It is a colourless, oily, coniine-like liquid, b.p. 173°–174°, $D^{24\cdot3°}$ 0·8318 and $[\alpha]_D^{24\cdot3°}$ + 81·33°. The ordinary salts are crystalline ; the hydrochloride, B.HCl, forms masses of needles, m.p. 188° ; the platinichloride, $B_2.H_2PtCl_6$, has m.p. 158°.

N-**Methyl-l-coniine** was obtained by Ahrens [4] from residues left in the preparation of coniine by crystallisation of the hydrobromides, that of d-coniine being much less soluble in water, or by converting coniine into the nitroso-compound. It is a colourless, coniine-like liquid, b.p. 175·6°/767 mm., $D_{20°}^{20°}$ 0·8349, $[\alpha]_D^{20°}$ — 81·92°. The hydrochloride, B.HCl, crystallises in leaflets, m.p. 191°–192°, the hydrobromide, B.HBr, forms leaflets, m.p. 189°–190° ; the platini-chloride in orange crystals, m.p. 153°–154° ; the aurichloride in brilliant leaflets, m.p. 77°–78°, and the picrate in long needles, m.p. 121°–122°.

A N-methylconiine, which was not well characterised, was obtained by Passon [5] by methylating d-coniine with potassium methyl sulphate. Hess and Eichel [6] have shown that d-coniine with formaldehyde and formic acid yields an active d-N-methyl-coniine, and that methyl*iso*pelletierine hydrazone (*see* p. 42) yields dl-N-methylconiine when heated with sodium ethoxide at 150°–170°.

Conhydrine, $C_8H_{17}ON$. This oxygenated alkaloid was first found in hemlock by Wertheim.[7] In the extraction of coniine from hem-lock (p. 31) conhydrine is also removed and may be separated by freezing it out, or by distilling the crude coniine, when conhydrine remains in the retort if the temperature is kept below 190°.

It crystallises in colourless leaflets and is a strongly basic substance, m.p. 121°, b.p. 226°, $[\alpha]_D$ + 10°. It is soluble in alcohol or chloroform, moderately so in water, and sparingly in

[1] Planta and Kekulé, *Annalen,* 1854, **89,** 150.
[2] *Berichte,* 1894, **27,** 2615.
[3] *Ibid.* 1905, **38,** 3108 ; 1917, **50,** 1477.
[4] *Ibid.* 1902, **35,** 1330.
[5] *Ibid.* 1891, **24,** 1678.
[6] *Ibid.* 1917, **50,** 1386.
[7] *Annalen,* 1856, **100,** 1329.

ether, from which it crystallises readily. The salts are crystalline ; the aurichloride, small rhombs or prisms, has m.p. 133°.

Constitution. Conhydrine yields a benzoyl derivative, m.p. 132°. On oxidation with chromic acid it is converted into *l*-piperidine-2-carboxylic acid, which indicates that the hydroxyl group of the alkaloid is in the side-chain, whence Willstätter [1] suggested formula (I) for conhydrine. The substance corresponding to this formula has, however, been synthesised by Löffler and Tschunke,[2] and shown not to be identical with conhydrine, and on this ground these authors have revived the alternative formula (II), first suggested by Engler and Baur,[3] and this has received confirmation from Hess and Eichel's

$$
\begin{array}{cc}
\text{(I)} & \text{(II)}
\end{array}
$$
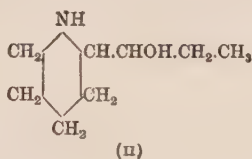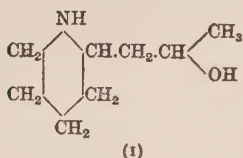
observation [4] that *N*-methylconhydrine, obtained by methylating the alkaloid with formaldehyde and formic acid, yields on oxidation with chromic acid 2-piperidyl ethyl ketone (the methyl group attached to the *N*-atom being lost) which on methylation with methyl sulphate furnishes *N*-methyl-2-piperidyl ethyl ketone identical with methyl*iso*pelletierine (*see* p. 42).

Though conhydrine is dextrorotatory it is convertible through β-conicëine (p. 37) into *l*-coniine (p. 32).

ψ-Conhydrine, $C_8H_{17}ON$, was found in hemlock by Merck and was examined by Ladenburg and Adam.[5] It closely resembles its isomeride conhydrine, with which it occurs as a residue after the removal of the liquid alkaloids by distillation (*see* p. 31), and from which it can be separated by crystallising the mixed hydrochlorides, that of conhydrine being very hygroscopic, whilst the ψ-conhydrine salt crystallises well from alcohol. The base was re-examined by Löffler,[6] and many of the data recorded regarding it shown to be inaccurate. It crystallises from dry ether in slender needles, m.p. 105°–106°, b.p. 236°–236·5°, $[\alpha]_D + 10·98°$ to $+ 11·06°$, or from wet ether in plates, m.p. 80° (*approx.*), and is a strongly alkaline base. The hydrochloride has m.p. 212°–213°; the aurichloride, $B . HAuCl_4$,

[1] *Berichte*, 1901, **34**, 3166.
[2] *Ibid.* 1909, **42**, 929.
[3] *Ibid.* 1894, **27**, 1777.
[4] *Ibid.* 1917, **50**, 1386.
[5] *Ibid.* 1891, **24**, 1071.
[6] *Ibid.* 1909, **42**, 116.

m.p. 133°–134° ; the platinichloride, m.p. 185°–186°, forms slender golden-yellow needles.

ψ-Conhydrine is a hydroxyconiine since on treatment with hydriodic acid it yields an iodoconiine, which on reduction forms d-coniine.   With phosphoric oxide it gives ψ-conicëine, $C_8H_{15}N$ (*see* p. 37). ψ-Conhydrine is not stereoisomeric with conhydrine, but according to Löffler probably contains the hydroxyl group in the pyridine nucleus thus :

NH

CH$_2$ CH.CH$_2$.CH$_2$.CH$_3$

CH$_2$ CH$_2$

CHOH

ψ-*Conhydrine* (Löffler)
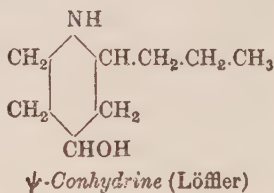
Willstätter's observation [1] that ψ-conhydrine, like conhydrine, yields piperidine-2-carboxylic acid on oxidation is difficult to reconcile with this formula, but is possibly due to the use of impure ψ-conhydrine.

γ-**Conicëine,** $C_8H_{15}N$. This base was isolated by Wolffenstein from commercial coniine by the method already described.[2]   In using von Braun's method of separation the γ-conicëine on benzoylation passes into benzoyl-δ-aminobutyl propyl ketone, COPh.NH. $CH_2.CH_2.CH_2.CH_2.CO.C_3H_7$, which remains with the benzoyl-coniine after extraction of the tertiary bases, and can be partly separated from it by concentrating the ethereal solution and pouring into light petroleum in which it is insoluble.   The rest remains in the flask, from which the benzoylconiine is distilled.   It yields conicëine on heating with hydrochloric acid at 120°.

γ-Conicëine is a coniine-like oil, b.p. 171°–172°/746 mm., $D^{22\cdot5°}$ 0·8825, almost insoluble in water, strongly alkaline and optically inactive.   Its salts are crystalline ; the hydrochloride, m.p. 143°, is hygroscopic ; the hydrobromide, m.p. 139°, is readily soluble in acetone ; the aurichloride, m.p. 69°, and the picrate, m.p. 72°, are precipitated as oils, but soon become crystalline. The platinichloride has m.p. 192°.   The cadmium iodide salt, B.HI.CdI$_2$, m.p. 146°–147°, crystallises from water in long needles.

γ-Conicëine is a secondary base, and on reduction yields *dl*-

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[1] *Berichte*, 1901, **34**, 3166.
[2] *Ibid*. 1895, **28**, 302.

coniine. It was prepared by Hofmann by the action of alkalis on bromoconiine, and, according to Löffler, is formed by the action of fuming hydrochloric acid on conhydrine (p. 34). These reactions are explained by formula (1) below, suggested by Lellmann and Wolffenstein. γ-Conicëine has been synthesised by Gabriel by hydrolysing δ-phthaliminobutyl propyl ketone.[1]

Conicëines. Six of these products have been obtained in various ways from coniine, bromo- or iodo-coniine, conhydrine and ψ-conhydrine ; their names and chief characters are as follows [2] : α-, β-, and γ-*Conicëines*, produced simultaneously by the action of fuming hydrochloric acid at 220° on conhydrine [3] ; with phosphoric oxide β-*conicëine* is the chief product, and no α-conicëine is formed.[4] Löffler assigned formula [IV] to α-conicëine,[5] but subsequently transferred it to ε-conicëine (*see below*). According to Löffler and Friedrich,[6] β-conicëine is *l*-2-allylpiperidine. On reduction with sodium in alcohol it yields *l*-coniine.

The constitution of γ-conicëine has been discussed above.

δ-*Conicëine* is formed by the action of sulphuric acid on bromoconiine. Formula [III] was assigned by Lellmann [7] to δ-conicëine, and this has been confirmed by synthesis of the inactive form of this base by Löffler and collaborators [8] by reducing 2-piperolidone, obtained by distilling piperidylpropionic acid.

ε-*Conicëine* is formed by the action of alkalis on iodo- or bromoconiine. Lellmann's ε-conicëine has been shown by Löffler [9] to be a mixture of two stereoisomeric bases having formula [IV]. ε-Conicëine contains two asymmetric carbon atoms, and the two forms consist of the stereoisomerides (— —) and (+ —), and may be separated by crystallisation of the *d*-tartrates. This bicyclic system has been named conidine by Löffler, and the two isomerides are called 2-methylconidine and *iso*-2-methylconidine.

ψ-*Conicëine* is obtained by dehydrating ψ-conhydrine with phosphoric oxide.[10]

[1] *Berichte*, 1909, **42**, 4059.
[2] Hofmann, *ibid.* 1885, **18**, 16, 27, 112 ; Lellmann, *Annalen*, 1890, **259**, 197.
[3] Löffler and Tschunke, *Berichte*, 1909, **42, 929.**
[4] *Berichte*, 1905, **38, 3326.**
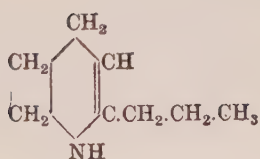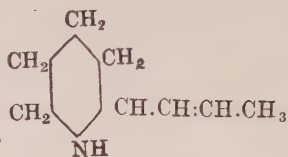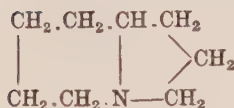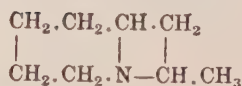[5] *Ibid.* 1904, **37,** 1879.
[6] *Ibid.* 1909, **42,** 107.
[7] *Annalen*, 1890, **259,** 193.
[8] *Berichte*, 1909, **42,** 94, 3420.
[9] *Ibid*, 1909, **42,** 948.
[10] Löffler, *ibid*. 1909, **42,** 116.

$$CH_2$$
$$CH_2 \diagup \diagdown CH$$
$$CH_2 \diagdown \diagup C.CH_2.CH_2.CH_3$$
$$NH$$

(I.) *γ-Coniceine*

$$CH_2$$
$$CH_2 \diagup \diagdown CH_2$$
$$CH_2 \diagdown \diagup CH.CH{:}CH.CH_3$$
$$NH$$

(II.) *β-Coniceine*

$$CH_2.CH_2.CH.CH_2$$
$$\qquad\qquad\qquad {>}CH_2$$
$$CH_2.CH_2.N{-}CH_2$$

(III.) *δ-Coniceine*

$$CH_2.CH_2.CH.CH_2$$
$$CH_2.CH_2.N{-}CH.CH_3$$

(IV.) *ε-Coniceine*

The principal properties of the isomerides are shown in the following table :

Name	Boiling-point	Melting-point of aurichloride	Specific rotation, $[\alpha]_D$	Relative density	Amino-character
α-Coniceine	158°	196°	+ 18·4°	0·8930 at 15°	Tertiary
β-Coniceine	168° (m.p. 41°)	122·5°	− 52·99°	0·8519 at 50°	Secondary
γ-Coniceine	171°–172°	69°	inactive	0·8825 at 22·5°	Secondary
l-δ-Coniceine	158°	207°	lævorotatory	0·896 at 23°	Tertiary
i-δ-Coniceine	161°	192°	inactive	0·904 at 15°	Tertiary
ε-Coniceine composed of	150°–151°	178°	+ 42·34°	0·8836 at 15°	Tertiary
2-methylconidine and	151°–154°	167°–168°	+ 67·4°	0·8856 at 15°	Tertiary
iso-2-methyl-conidine	143°–145°	198°–199°	− 87·34°	0·8624 at 15°	Tertiary
ψ-Coniceine	171°–172°	(oily)	+ 122·6°	0·8776 at 15°	Secondary

Physiological Action of Hemlock Alkaloids. All the alkaloids contained in hemlock are poisonous. They produce paralysis of the motor nerve terminations and stimulation followed by depression of the central nervous system, though some authorities maintain that they exert little or no central action. They cause nausea and vomiting at an early stage of their action. In frogs they have a curare-like action on motor nerve terminations, but in mammals this is exhibited to a much less extent. Large doses cause slowing of the heart's action. Respiration is generally accelerated and deepened at first, but eventually becomes slow and laboured, and finally ceases, while the heart is still strong and consciousness has just disappeared. According to Albahary and Löffler [1] *d*- and

[1] *Compt. rend.* 1908, **147**, 996.

l-coniines are identical in physiological activity. By the introduction of a double linking, as in γ-conicëine, the toxicity is greatly increased, whilst by the insertion of a hydroxyl group, as in the conhydrines, it is much reduced.

ALKALOIDS OF POMEGRANATE ROOT BARK

The root bark of the pomegranate tree (*Punica granatum*) employed in medicine as an anthelmintic, was first investigated by Tanret,[1] who isolated from it four alkaloids, to which a fifth, *iso*-methylpelletierine was added by Piccinini.[2]   Two of Tanret's alkaloids, pelletierine and methylpelletierine were optically active, and, in that respect alone, the former differed from *iso*pelletierine. K. Hess and A. Eichel,[3] being unable to find any optically active alkaloid in the bark, have applied the name pelletierine to Tanret's *iso*pelletierine, and having shown that Tanret's methylpelletierine is identical with Piccinini's *iso*methylpelletierine and that the latter is a methyl derivative of a base isomeric with pelletierine, have renamed it methyl*iso*pelletierine. This reduced the number of alkaloids from five to three, viz.: *Pelletierine*, $C_8H_{15}ON$ (*iso*pelletierine of Tanret) ; *pseudopelletierine*, $C_9H_{15}ON$; methyl*iso*pelletierine, $C_9H_{17}ON$ (methylpelletierine of Tanret, *iso*methylpelletierine of Piccinini). But the same workers [4] have recently added two more, viz. : iso*Pelletierine*, $C_8H_{15}ON$; α-N-*methylpiperidyl*-2-*propan*-β-*one*, $C_9H_{17}ON$, so that the total again stands at five.

The alkaloids may be prepared [5] by extracting a finely ground mixture of the bark and slaked lime with water, exhausting this extract with chloroform, and the chloroform in turn with hydrochloric acid. The acid liquid is made alkaline with caustic soda, extracted with ether, the ethereal extract dried over potassium hydroxide, filtered, the ether distilled off and the residue distilled under a pressure of 15 to 20 mm., when pelletierine and methyl*iso*-pelletierine distil together at 100°–120°, and pseudopelletierine at 145°, or the distillation may be stopped when 145° is reached, and pseudopelletierine isolated by dissolving the residue in light petroleum and cooling the solution in ice water. From the mixture of pelle-

[1] *Compt. rend.* 1878, **86**, 1270 ; 1879, **88**, 716 ; 1880, **90**, 696.

[2] *Gazzetta,* 1899, **29**, ii, 311.

[3] *Berichte,* 1917, **50**, 1386; *cf.* however, Tanret, *Compt. rend.* 1920, **170**, 1118.

[4] *Loc. cit.* and *ibid.* 1919, **52**, 1005 ; 1917, **50**, 380.

[5] Tanret, *loc. cit.* ; Hess, *Berichte,* 1917, **50**, 1395 ; 1919, **52**, 1005.

tierine and methyl*iso*pelletierine the bulk of the former is separated
as the hydrobromide. The residual liquor is treated with ethyl
chloroformate, to convert the rest of the pelletierine into the corre-
sponding urethane (from which the alkaloid can be regenerated by
heating with hydrochloric acid at 125°–130°). The unattacked
bases are then separated by fractional distillation under reduced
pressure : α-*N*-methylpiperidyl-2-propan-β-one boils at 82°–84°/19
mm., and is purified as the picrate and methyl*iso*pelletierine at
114°–117°/26 mm. *iso*Pelletierine urethane (with some pelle-
tierine urethane) boils at 150°–165°/13 mm., and this final mixture
is separated by boiling with caustic soda in alcohol when the pelle-
tierine is resinified and the *iso*pelletierine, left unaffected, is recover-
able by distillation.

According to Ewers [1] the root bark contains 0·6 to 0·7 per cent.
of total alkaloids and the stem bark 0·5 per cent.

By the process described above, K. Hess [2] obtained, per kilo-
gramme of bark, pelletierine 0·52, pseudopelletierine 1·8, methyl-
*iso*pelletierine 0·2, *iso*pelletierine 0·01, and α-*N*-methylpiperidyl-
2-propan-β-one 0·01 grm.

Pelletierine, $C_8H_{15}ON$. It has already been explained that this
name is now used for *dl*-pelletierine, identical with Tanret's *iso ·*
pelletierine. The point is still in dispute whether pelletierine
occurs in the plant in an optically active form.[3]

The optically inactive base is a colourless oil, boiling at 106°/21
mm., and readily absorbs oxygen, becoming dark and resinous ; it
is soluble in water, ether, or chloroform, and is alkaline in reaction.
The hydrochloride has m.p. 143°–144°, and is not hygroscopic ; the
hydrobromide forms well-developed, fan-like clusters, m.p. 140° ;
the picrate melts at 150°–151°. By slow evaporation of an aqueous
solution of the *d*-acid tartrate, Hess and Eichel [3] have resolved the
base into *d*- and *l*-forms, the latter being finally purified through the
lævo-acid tartrate. *d*-Pelletierine *d*-acid tartrate has m.p. 129°,
$[\alpha]_D^{20°} + 21·0°$ in alcohol, and the sulphate $[\alpha]_D^{18°} + 5·86°$.

l-Pelletierine *l*-acid tartrate has m.p. 129°, $[\alpha]_D^{20°} - 20·94°$, and
the sulphate $[\alpha]_D^{18°} - 5·89°$. Tanret originally described natural
pelletierine as dextrorotatory and giving lævorotatory salts, but has
recently assigned to the free base the specific rotation $- 31·1°$, and
has described a number of salts, all of which are lævorotatory, but

[1] *Arch. Pharm.* 1899, **237**, 49.
[2] *Berichte*, 1919, **52**, 1005.
[3] *Ibid.* 1918, **51**, 741; *cf.* Hess and Weltzien, *ibid.* 1920, **53**, 119.

the N-acetyl and N-benzoyl derivatives have $[\alpha]_D + 32 \cdot 6°$ and $+ 18 \cdot 7°$ respectively, whilst the semicarbazone hydrochloride, m.p. $168°$–$170°$, has $[\alpha]_D - 10 \cdot 8°$.[1]

Constitution of Pelletierine.   The oxygen atom of the alkaloid is present in the form of an aldehyde group,[2] since the base yields an oxime, convertible by the action of phosphorus pentachloride into a nitrile, b.p. $104°$–$106°/15$ mm., which is hydrolysed by caustic potash in alcohol into an acid, the ethyl ester of which is Löffler and Kaim's[3] ethyl β-2-piperidylpropionate, $C_5H_{10}N \cdot CH_2 \cdot CH_2 \cdot COOC_2H_5$, which contains one oxygen atom more than pelletierine, though the latter is not directly oxidisable to this acid.

Further, pelletierine yields a liquid hydrazone, b.p. $150°/20$ mm., which on reduction with sodium in alcohol at $156°$–$170°$ is converted into *dl*-coniine.   These reactions are explained by the following formulæ,[2] in which pelletierine is represented as the aldehyde (β-2-piperidylpropionaldehyde) of coniine.   In confirmation of this

β-2-*piperidylpropionic acid*   *Pelletierine*   *Coniine*
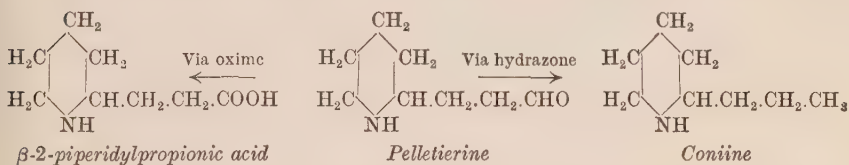
formula for pelletierine it should be noted that the alkaloid behaves as a secondary base, and can be methylated by heating with form-aldehyde and formic acid at $135°$–$143°$, yielding a methylpelletierine not identical with Piccinini's *iso*methylpelletierine (methyl*iso*-pelletierine of Hess).

*iso***Pelletierine,** $C_8H_{15}ON$.   This name, originally applied by Tanret to a base which must now be regarded as *dl*-pelletierine, has been adopted by K. Hess[4] for a new alkaloid recently isolated from pomegranate root bark.   This is an oily liquid having b.p. $102°$–$107°/11$ mm., $[\alpha]_D \pm 0°$; the hydrobromide melts at $149°$, and the picrate at $154°$.   This new *iso*pelletierine is also obtained by de-methylation of methyl*iso*pelletierine and is re-convertible into the latter by the action of methyl sulphate.   Its constitution is discussed under methyl*iso*pelletierine (*see* p. 42).

Methylpelletierine, $C_9H_{17}ON$, was originally described by Tanret as an oily liquid, b.p. $215°$, giving a hydrochloride having $[\alpha]_D + 22°$.

[1] *Compt. rend.* 1920, **170**, 1118.
[2] Hess and Eichel, *Berichte*, 1917, **50**, 1192.
[3] *Berichte*, 1909, **42**, 97.
[4] *Ibid.* 1919, **52**, 1005.

It has been re-examined recently by the same author with the following results : b.p. 106°–108°/45 mm., $[\alpha]_D + 27 \cdot 7°$ (in aqueous solution $+ 24 \cdot 1°$) ; hydrochloride, m.p. 168°–170°, $[\alpha]_D + 41 \cdot 2°$; hydrobromide, m.p. 165°–167°, $[\alpha]_D + 33 \cdot 5°$; sulphate, $[\alpha]_D + 38°$; picrate, m.p. 157°–159°, and platinichloride, m.p. 206°–208°.[1] According to Hess and Eichel, it is identical with methyl*iso*pelletierine.

Methyl*iso*pelletierine, $C_9H_{17}ON$. This base was isolated by Piccinini under the name *iso*methylpelletierine and was subsequently re-examined by K. Hess [2] and his colleagues (*see* p. 39).   It is an oily liquid, b.p. 114°–117°/26 mm., of strongly alkaline reaction, miscible with water in all proportions and optically inactive.   It can be resolved into *d*- and *l*- forms having b.p. 109°/24 mm., and specific rotations $[\alpha]_D^{18°}$ of 6·7° and 9·9° in dilute sulphuric and hydrochloric acids respectively.   *d*-Methyl*iso*pelletierine *d*-bitartrate has m.p. 133°–134° and $[\alpha]_D^{20°} + 22 \cdot 7°$, and the optical antipode has m.p. 132°–134° and $[\alpha]_D^{18°} - 20 \cdot 3°$, whilst the two hydrochlorides have $[\alpha]_D^{18°} + 11 \cdot 08°$ and $- 10 \cdot 64°$ respectively.   The hydrochloride has m.p. 156°, hydrobromide m.p. 151°–152° ; the picrate melts at 158°, and the aurichloride forms orange-yellow rosettes, m.p. 115°–117°.

The alkaloid yields a semicarbazone, m.p. 169°, which forms large transparent crystals soluble in alcohol and insoluble in ether, a liquid hydrazone, b.p. 154°–155°/29 mm., and a liquid oxime, b.p. 160°/12 mm., from which a crystalline picrate, m.p. 106°, can be prepared.   The methiodide crystallises in cubes, m.p. 156°.

On oxidation with chromic acid in sulphuric acid solution the base yields N-methylpiperidine-2-carboxylic acid, $MeN \cdot C_5H_9 \cdot COOH$, whilst the hydrazone (*see above*) on reduction with sodium in ethyl alcohol at 150°–170° forms *dl*-methylconiine (*see* p. 34).

In view of these reactions methyl*iso*pelletierine must have one of the structures represented by the formula :

$$CH_2 \begin{array}{c} CH_2-CH_2 \\ \diagdown \\ CH_2-NCH_3 \end{array} CHX$$
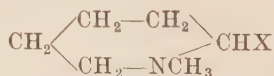
in which X may be (a) $- CH_2 \cdot CH_2 \cdot CHO$; (b) $- CH_2 \cdot CO \cdot CH_3$; or (c) $- CO \cdot CH_2 \cdot CH_3$. If X were represented by (a), methyl*iso*pelletierine should be produced when pelletierine is methylated, which is not the case ; if it were represented by (b) the base would be α-N-
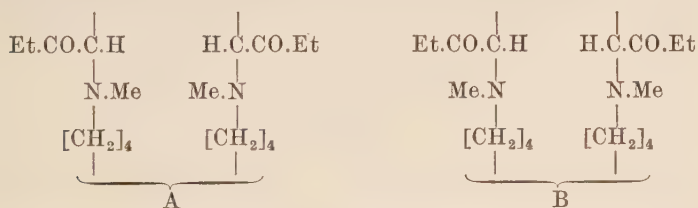
[1] *Compt. rend.* 1880, **90,** 696 ; 1920, **170,** 1118.
[2] *Berichte,* 1917, **50,** 344, 1386 ; 1918, **51,** 741 ; 1919, **52,** 964, 1005.

methylpiperidyl-2-propan-β-one, which has been synthesised and found to be different.[1] It must, therefore, be represented by (*c*). This formula brings methyl*iso*pelletierine and *iso*pelletierine into close relationship with the hemlock alkaloids thus :

1. coniine = 2-piperidylpropane   *N*-methyl derivative = methyl-coniine.

2. *iso*pelletierine = 2-piperidylpro-pane-α-one   *N*-methyl derivative = methyl-*iso*pelletierine.

3. conhydrine = 2-piperidyl-α-hydroxypropane

4. conhydrinone = 2-piperidyl-propane-α-one

     N-methylconhydrinone and methyl*iso*pelletierine.

It has been pointed out already that methyl*iso*pelletierine is convertible into methylconiine by reduction of its hydrazone, and it should be possible by methylating conhydrine and oxidising the methylconhydrine formed, to obtain methylconhydrinone, which should be identical with methyl*iso*pelletierine. The substance actually formed in the oxidation is conhydrinone—the methyl group attached to the nitrogen atom being lost—and this on methylation yields two isomeric *N*-methyl derivatives, viz., methyl*iso*pelletierine and *N*-methylconhydrinone. Both are optically inactive and resolvable, though only the 2-carbon atom in the ring is asymmetrical.[2] To explain this unexpected isomerism, Hess [3] has revived in a slightly different form Ladenburg's suggestion of asymmetry due to a tervalent nitrogen atom. On this basis it is possible to represent the two pairs of optically active isomerides derivable from *dl*-methyl-*iso*pelletierine and *dl*-methylconhydrinone as follows : [4]

$$
\begin{array}{cccc}
\text{Et.CO.}\overset{|}{\text{C}}\text{.H} & \text{H.}\overset{|}{\text{C}}\text{.CO.Et} & \text{Et.CO.}\overset{|}{\text{C}}\text{.H} & \text{H.}\overset{|}{\text{C}}\text{.CO.Et} \\
\overset{|}{\text{N}}\text{.Me} & \text{Me.}\overset{|}{\text{N}} & \text{Me.}\overset{|}{\text{N}} & \overset{|}{\text{N}}\text{.Me} \\
[\text{C}\overset{|}{\text{H}}_2]_4 & [\text{C}\overset{|}{\text{H}}_2]_4 & [\text{C}\overset{|}{\text{H}}_2]_4 & [\text{C}\overset{|}{\text{H}}_2]_4 \\
\underbrace{\hspace{3em}}_{\text{A}} & & \underbrace{\hspace{3em}}_{\text{B}} &
\end{array}
$$

Of these pairs A is taken to represent the methyl*iso*pelletierines, since they give semicarbazones more easily than the isomeric pair. So far it has not been possible to interconvert methyl*iso*pelletierine

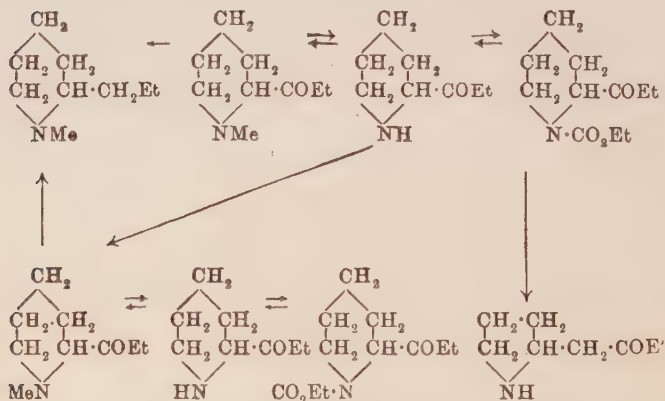[1] K. Hess, A. Eichel and C. Uibrig, *Berichte*, 1917, **50,** 351.

[2] K. Hess and E. Eichel, *ibid.* 1917, **50,** 1386.

[3] *Ibid.* 1919, **52,** 964.

[4] *Ibid.* 1919, **52, 964,** 1622 ; 1920, **53,** 129.

and methylconhydrinone, but their hydrazones on boiling with sodium ethoxide in alcohol both yield *dl*-methylconiine, whilst on demethylation with ethyl azodicarboxylate, each yields its characteristic demethylated product, viz., *iso*pelletierine and conhydrinone, *i.e.*, a change at the *N*-atom preserves the particular structure, whilst one at the asymmetric carbon atom leads to the same product in both cases if the oxygen atom in the side chain disappears at the same time. *iso*Pelletierine and conhydrinone each yield a characteristic ethylurethane, but whilst the one is hydrolysed slowly by boiling aqueous alcoholic sodium hydroxide to *iso*pelletierine, the other is quickly and quantitatively converted by the same means into *dl*-α-2-pyrrolidylbutane-β-one.

These interchanges are shown by the following formulæ :

$$
\begin{array}{cccccc}
\text{CH}_2 & & \text{CH}_2 & & \text{CH}_2 & & \text{CH}_2 \\
\text{CH}_2\ \text{CH}_2 & \leftarrow & \text{CH}_2\ \text{CH}_2 & \rightleftharpoons & \text{CH}_2\ \text{CH}_2 & \rightleftharpoons & \text{CH}_2\ \text{CH}_2 \\
\text{CH}_2\ \text{CH·CH}_2\text{Et} & & \text{CH}_2\ \text{CH·COEt} & & \text{CH}_2\ \text{CH·COEt} & & \text{CH}_2\ \text{CH·COEt} \\
\text{NMe} & & \text{NMe} & & \text{NH} & & \text{N·CO}_2\text{Et}
\end{array}
$$

$$
\begin{array}{cccc}
\text{CH}_2 & \text{CH}_2 & \text{CH}_2 & \\
\text{CH}_2\ \text{CH}_2 & \text{CH}_2\ \text{CH}_2 & \text{CH}_2\ \text{CH}_2 & \text{CH}_2·\text{CH}_2 \\
\text{CH}_2\ \text{CH·COEt} & \text{CH}_2\ \text{CH·COEt} & \text{CH}_2\ \text{CH·COEt} & \text{CH}_2\ \text{CH·CH}_2·\text{COE'} \\
\text{MeN} & \text{HN} & \text{CO}_2\text{Et·N} & \text{NH}
\end{array}
$$

α-*N*-**Methylpiperidyl-2-propanone,**　　NCH$_3$.C$_5$H$_9$.CH$_2$.CO.CH$_3$. This isomeride of methyl*iso*pelletierine was obtained in minute quantity in the first runnings from the fractionation of crude pelletierine by K. Hess and A. Eichel. It had already been synthesised by Hess, Merck and Uibrig, by the action of formaldehyde on γ-2-piperidylpropyl alcohol in presence of hydrochloric acid. It is a colourless oil, b.p. 82°-84°/19 mm., yielding an aurichloride, prisms, m.p. 115°-116° and a picrate, yellow needles, m.p. 160°-161°.[1]

Pseudopelletierine, C$_9$H$_{15}$ON (N-*Methylgranatonine*). This, the best-known of the pomegranate bark alkaloids, was isolated by Tanret in 1879, and is dealt with last because its constitution is

[1] *Berichte*, 1917, **50**, 380; *cf. ibid.* 1915, **48**, 1886.

different from those of the alkaloids just described, and brings it into relationship with the tropane group (p. 62). It crystallises from light petroleum in anhydrous, prismatic tablets, m.p. 48°, b.p. 246°, $[\alpha]_D$ 0°, dissolves readily in ether, alcohol, or chloroform, less readily in light petroleum. Pseudopelletierine is a strong base and gives well-crystallised salts ; the hydrochloride, B.HCl, forms rhombohedra ; the platinichloride, $B_2.H_2PtCl_6$, forms reddish needles, and the aurichloride is a yellowish crystalline substance. The picrate is readily soluble in water. The base is precipitated by all the ordinary alkaloidal reagents, and with chromic acid gives an intense green coloration.
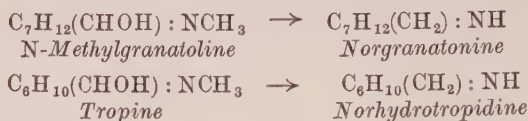
Constitution. The alkaloid behaves with methyl iodide as a tertiary base, forming pseudopelletierine methiodide, colourless cubes, m.p. above 280°. It forms an oxime crystallising in tablets, m.p. 128°, and on reduction is converted into its secondary alcohol, *N*-methylgranatoline, $C_9H_{17}ON$. This crystallises from light petroleum in fine needles, melting at 100°, and distils at 251°. It forms a monobenzoyl derivative, and when heated with hydriodic acid gives *N*-methylgranatyliodide, $C_9H_{16}NI$. The latter, on longer heating with the reagent, loses a molecule of hydriodic acid and forms the unsaturated *N*-methylgranatenine, $C_9H_{15}N$. This series of changes may be represented thus [1] :

Pseudo- *pelletierine*	*N-methyl-* *granatoline*	*N-methyl-* *granatyliodide*	*N-methyl-* *granatenine*

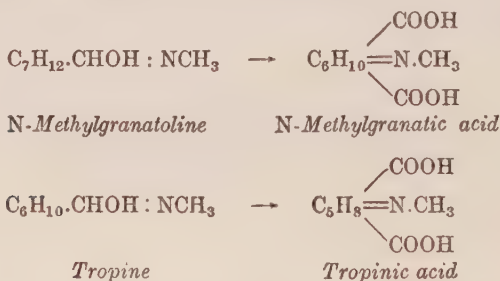|			
Tropinone	*Tropine*	*Iodotropine*	*Tropidine*
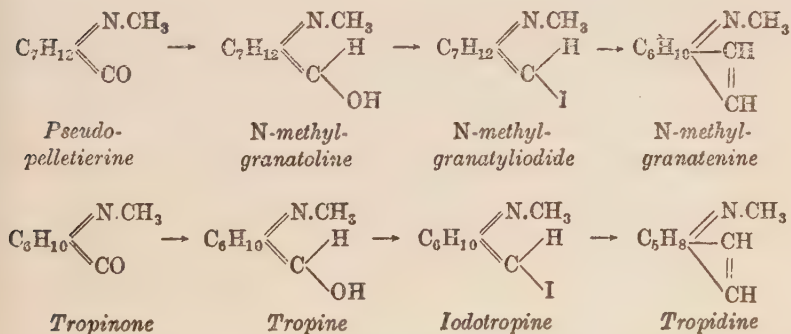
On comparing these reactions with those brought about by similar means in the tropane group (p. 74), it is evident that a close parallelism exists which suggests that pseudopelletierine is a next higher homologue of tropinone. This similarity in behaviour is also

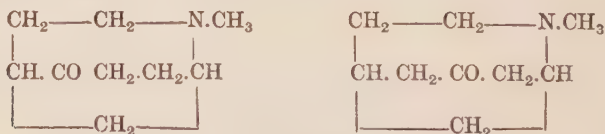[1] Ciamician and Silber, *Berichte*, 1892, **25**, 1601 ; 1893, **26**, 156, 2740.

shown in the conversion of N-methylgranatoline into *norgranatonine* by the prolonged action of hydriodic acid and phosphorus : [1]

$$C_7H_{12}(CHOH):NCH_3 \quad \rightarrow \quad C_7H_{12}(CH_2):NH$$
N-*Methylgranatoline*   *Norgranatonine*

$$C_6H_{10}(CHOH):NCH_3 \quad \rightarrow \quad C_6H_{10}(CH_2):NH$$
Tropine   *Norhydrotropidine*

Similarly N-methylgranatoline, on oxidation with permanganate, furnishes N-methylgranatic acid, just as tropine yields tropinic acid.

$$C_7H_{12}.CHOH:NCH_3 \quad \rightarrow \quad C_6H_{10}{=}N.CH_3 \Big\langle \begin{matrix} COOH \\ COOH \end{matrix}$$

N-*Methylgranatoline*   N-*Methylgranatic acid*

$$C_6H_{10}.CHOH:NCH_3 \quad \rightarrow \quad C_5H_8{=}N.CH_3 \Big\langle \begin{matrix} COOH \\ COOH \end{matrix}$$

Tropine   *Tropinic acid*

This similarity in reaction has led to the adoption for pseudopelletierine of formulæ based on those from time to time assigned to tropinone,[2] thus :

```
CH2——CH2——N.CH3        CH2——CH2——N.CH3
  |          |            |          |
CH. CO  CH2.CH2.CH      CH. CH2. CO. CH2.CH
  |          |            |          |
  └——CH2——┘              └———CH2——┘
```

Pseudopelletierine
(I) *Ciamician and Silber*   (II) *Piccinini*

The change from (I) to (II) was due to Piccinini's observation that pseudopelletierine reacts with amyl nitrite to form a di*iso*nitroso derivative,[3] indicating the presence of the group $-CH_2-CO-CH_2$.
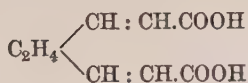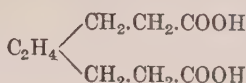
The same author has further modified this formula as the result of the study of the exhaustive methylation of pseudopelletierine [4] in which the final stages are the conversion of the dimethyl ester of N-methylgranatate (*see above*) into the dimethyl ester of N-methyl-granatenic acid, $C_6H_9(NMe_2):(COOMe)_2$, and the methiodide of this on boiling with caustic alkali yields trimethylamine and homopi-perylenedicarboxylic acid, which on reduction furnishes suberic acid.

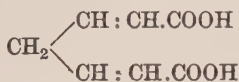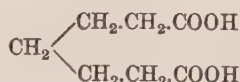[1] Ciamician and Silber, *Berichte*, 1894, **27,** 1851.
[2] *Cf. ibid.* 1894, 27, 2860 ; 1896, **29,** 482.
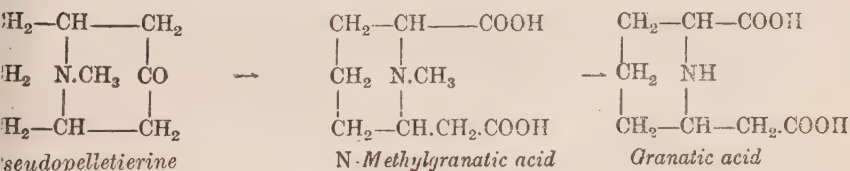[3] *Gazzetta*, 1899, **29,** i, 408 ; ii, 115.
[4] *Ibid.* 1899, **29,** ii, 104.

$$C_2H_4 \Big\langle \begin{matrix} CH:CH.COOH \\ CH:CH.COOH \end{matrix} \qquad\qquad C_2H_4 \Big\langle \begin{matrix} CH_2.CH_2.COOH \\ CH_2.CH_2.COOH \end{matrix}$$

Homopiperylenedicarboxylic acid   *Suberic acid.*

Under like conditions tropinic acid yields piperylenedicarboxylic acid convertible into pimelic acid.

$$CH_2 \Big\langle \begin{matrix} CH:CH.COOH \\ CH:CH.COOH \end{matrix} \qquad\qquad CH_2 \Big\langle \begin{matrix} CH_2.CH_2.COOH \\ CH_2.CH_2.COOH \end{matrix}$$

Piperylenedicarboxylic acid   *Pimelic acid*

Piccinini has, therefore, adopted the following formula for pseudo-pelletierine,[1] which is derived from Willstätter's tropinone formula (p. 77) by change of a heptamethylene to an octomethylene ring. The degradation of the alkaloid to a simple pyridine derivative (granatic acid) may be represented thus :

$$
\begin{matrix}
CH_2-CH\!\!-\!\!-CH_2 \\
| \qquad | \qquad | \\
CH_2 \;\; N.CH_3 \;\; CO \\
| \qquad | \qquad | \\
CH_2-CH\!\!-\!\!-CH_2
\end{matrix}
\longrightarrow
\begin{matrix}
CH_2-CH\!\!-\!\!-COOH \\
| \qquad | \\
CH_2 \;\; N.CH_3 \\
| \qquad | \\
CH_2-CH.CH_2.COOH
\end{matrix}
\longrightarrow
\begin{matrix}
CH_2-CH-COOH \\
| \qquad | \\
CH_2 \;\; NH \\
| \qquad | \\
CH_2-CH-CH_2.COOH
\end{matrix}
$$

seudopelletierine   *N-Methylgranatic acid*   *Granatic acid*

Granatic acid, when heated at 150° with mercuric acetate and acetic acid, yields a 2-methylpyridinecarboxylic acid which, on distillation, furnishes 2-methylpyridine. It is interesting to note that pseudopelletierine is not so remote in structure from two of the alkaloids which accompany it in the bark as may appear at first sight, as the following formulæ show :

$$
\begin{matrix}
CH_2-CH\!\!-\!\!-CH_2 \\
| \qquad | \qquad | \\
CH_2 \;\; N.CH_3 \;\; CO \\
| \qquad | \qquad | \\
CH_2-CH\!\!-\!\!-CH_2
\end{matrix}
\qquad
\begin{matrix}
CH_2-CH\!\!-\!\!-CO \\
| \qquad | \qquad | \\
CH_2 \;\; N.CH_3 \;\; CH_2 \\
| \qquad | \qquad | \\
CH_2-CH_2 \;\; CH_3
\end{matrix}
\qquad
\begin{matrix}
CH_2-CH\!\!-\!\!-CH_2 \\
| \qquad | \qquad | \\
CH_2 \;\; NCH_3 \;\; CO \\
| \qquad | \qquad | \\
CH_2-CH_2 \;\; CH_3
\end{matrix}
$$

Pseudopelletierine   *Methylisopelletierine*   *α-N-Methylpiperidyl-2-propanone*
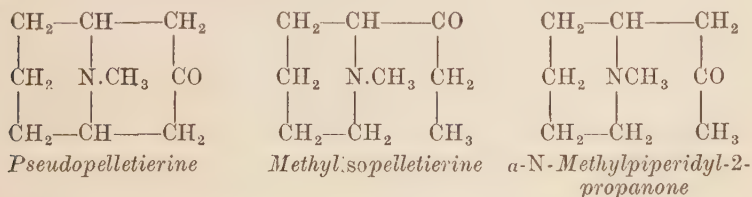
Physiological Action of Pomegranate Bark Alkaloids. Pomegranate root bark is official in the United States Pharmacopœia, but is now little used in medicine. The active constituent is believed

[1] *Real. Accad. Lincei*, 1899, [v], ii, 219   *cf.* Willstätter and Veraguth, *Berichte*, 1905, **38**, 1984.

to be pelletierine, which, according to Schroeder, is highly toxic
to tapeworms and explains the use of the bark as a vermifuge.
Crude mixtures of the tannates and sulphates of the alkaloids
have been employed in medicine under the names pelletierine
tannate and pelletierine sulphate. The former is official in the
British and United States Pharmacopœias.

ALKALOID OF *PIPER* SPECIES

Piperine, $C_{17}H_{19}O_3N$. This alkaloid, which occurs in several
plants belonging to the natural order Piperaceæ, was isolated in 1819
by Oersted from the fruits of *Piper nigrum,* which constitute the
black and white peppers of commerce. In 1879 Flückiger and
Hanbury [1] showed that it was also contained in the two varieties of
long pepper derived from *Piper longum* and *P. officinarum,* whilst in
1881 Stenhouse obtained it from Ashantee black pepper, consisting
of the fruits of *Piper Clusii.* The amount of piperine present varies
from 1 to 2 per cent. in long pepper to from 5 to 9 per cent. in black
and white pepper, and is of some importance as affording an indica-
tion of the freedom of the spice from adulterants. It may be
estimated approximately by mixing a weighed quantity of the
pepper into a stiff paste with slaked lime and water, drying this at
100°, and exhausting in a Soxhlet extractor with ether contained in
a tared flask. The ether is distilled off, the residue dried at 100°,
and weighed as piperine.

The alkaloid may be prepared by a similar process, but more
economically by exhausting the finely powdered fruits with 95 per
cent. alcohol, the solvent being removed by distillation, and the
extract so obtained shaken with solution of soda for the removal of
resin. The residue, on solution in boiling 95 per cent. alcohol, and
decolorisation with animal charcoal, deposits piperine on cooling.

The alkaloid crystallises from alcohol in monoclinic needles,
m.p. 128°–129·5°, $[\alpha]_D$ 0°, is slightly soluble in water, and more so in
alcohol, ether, or chloroform. The alcoholic solution has a pepper-
like taste. Solutions of piperine are not alkaline, and the base forms
salts only with strong acids ; the platinichloride, $B_4 . H_2PtCl_6$, forms
orange-red needles. Sulphuric acid gives a dark red solution with
piperine, and nitric acid, on warming, a resin which dissolves in
aqueous potash with a deep red colour. Iodine in potassium iodide
added to an alcoholic solution of the base in presence of a little

[1] *Pharmacographia*, p. 584.

hydrochloric acid gives a characteristic periodide, $B_2.HI.I_2$, crystallising in lustrous, steel-blue needles, m.p. 145°, slightly soluble in alcohol, easily so in chloroform. Piperine is rarely employed in medicine ; in action it is said to resemble quinine, but to be much less active and rather uncertain in effect.

Constitution. Anderson [1] observed that when boiled with alkalis, piperine was decomposed with the formation of a base and an acid, which were subsequently named by Babo and Keller [2] piperidine and piperic acid respectively.

$$C_{17}H_{19}O_3N + H_2O \quad = \quad C_5H_{11}N \quad + \quad C_{12}H_{10}O_4$$
$$\textit{Piperine} \qquad\qquad \textit{Piperidine} \qquad \textit{Piperic acid}$$

The basic decomposition product had already been obtained by Wertheim and Rochleider,[3] but its constitution was not ascertained with certainty until its synthesis was effected by Ladenburg from pentamethylenediamine, and by the reduction of pyridine, showing it to be hexahydropyridine.

Piperic acid, $C_{12}H_{10}O_4$, is insoluble in water, and crystallises from hot alcohol in long bright yellow needles, m.p. 217°. It readily takes up four atoms of bromine or hydrogen and is oxidised by potassium permanganate to piperonal, whilst on fusion with potash it furnishes protocatechuic, acetic, and oxalic acids. These and other reactions led Fittig [4] to assign to the acid the formula given below, the validity of which was proved by Ladenburg and Scholz,[5] who synthesised the acid by the following series of reactions. Protocatechuicaldehyde was treated with methylene iodide in presence of alcoholic potash, giving piperonal ; the latter by condensation with acetaldehyde in presence of caustic soda was converted into piperylacrolein, which in its turn with acetic anhydride (Perkin's reaction) gave piperic acid.

C.CH : CH.CHO   C.CH : CH.CH : CH.COOH

Piperylacrolein   *Piperic acid*
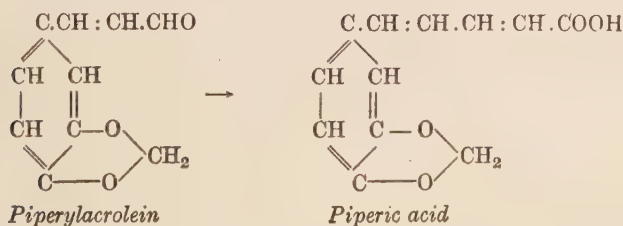
[1] *Annalen,* 1850, **75,** 82 ; **84,** 345.
[2] *Journ. prakt. Chem.* 1857, **72,** 53.
[3] *Annalen,* 1845, **54,** 255.
[4] *Ibid.* 1885, **227,** 31.
[5] *Berichte,* 1894, **27,** 2958.

Finally, as had already been shown by Rugheimer,[1] piperidine, when treated with piperoyl chloride in benzene solution, furnished piperine.

$$C_5H_{10}N.CO.CH : CH.CH : CH.C_6H_3.O_2CH_2$$
Piperine

Piperovatine, $C_{16}H_{21}O_2N$, isolated by Dunstan and Garnett [2] from *Piper ovatum* forms colourless needles, m.p. 123°, soluble in alcohol, but sparingly so in dry ether. The alkaloid forms no salts. When heated with water at 160° a volatile base, probably a pyridine derivative, is formed, together with an acid and an oil having the odour of anisole. Piperovatine is a temporary depressant of motor and sensory nerve fibres, and of sensory nerve terminations ; it depresses the heart's action, and in frogs induces tetanic convulsions similar to those produced by strychnine.

ALKALOIDS OF NICOTIANA SPECIES

Members of this series of alkaloids have, with one exception, only been found in Nicotiana species, of which *N. tabacum*, the source of commercial tobacco, exists in many cultural varieties. The observation [3] that Indian hemp contains nicotine is probably due to the use of this drug as prepared for smoking, for which purpose tobacco is commonly added. The exceptional instance is the Australian plant, *Duboisia Hopwoodii*, from which Liversedge [4] isolated the alkaloid piturine which Rothera [5] subsequently showed to be nicotine. Four alkaloids have been isolated from tobacco : *Nicotine*, $C_{10}H_{14}N_2$; *Nicotimine*, $C_{10}H_{14}N_2$; *Nicoteine*, $C_{10}H_{12}N_2$; *Nicotelline*, $C_{10}H_8N_2$.

According to Noga,[6] Turkish tobacco contains nicoteine, nicotelline, included in the foregoing list, and two others, *iso*nicoteine, $C_{10}H_{12}N_2$ and nicotoine, $C_8H_{11}N$. Pictet and Court have also found pyrrolidine and 1-methylpyrroline in tobacco. The quantity of alkaloids in tobacco shows great variation, but does not as a rule exceed 6 per cent., and averages about 4 per cent. In 1,026 parts of the total alkaloids from Kentucky tobacco, Pictet and Rotschy found 20 of nicoteine, 5 of nicotimine, and 1 of nicotelline, the rest

[1] *Berichte*, 1882, **15**, 1390.
[2] *Trans. Chem. Soc.* 1895, **67**, 94; *cf.* Dunstan and Carr, *Proc. Chem. Soc.* 1895, p. 177.
[3] Preobrachensky, *Pharm. Zeit.* 1876, p. 705.
[4] *Chem. News*, 1881, **43**, 124.
[5] *Bio-Chem. Journ.* 1910, **5**, 193.
[6] *Fachl. Mitt. öst. Tabakregie*, 1914 (*Chem. Soc. Abstr.* 1915 [i], 711).

being nicotine,[1] but, as these authors point out, the figures do not necessarily represent the proportions actually present in the plant.

For the isolation of the total alkaloids (commercial nicotine), the finely powdered tobacco leaves are exhausted with warm water or dilute acid, the extract concentrated, made alkaline by addition of a slight excess of lime or caustic soda, and steam-distilled. The distillate is neutralised, evaporated to a small bulk, made alkaline, and the liberated alkaloids shaken out with ether. The residue left after removal of the ether by distillation is dried in a current of hydrogen.[2] Commercial nicotine is generally made from waste tobacco, chiefly midribs, which are removed from the leaves in preparing tobacco for smoking. For use as an insecticide, large quantities of " tobacco extract " (an aqueous extract of waste tobacco) are manufactured, and this material is a convenient source of tobacco alkaloids.

Estimation. Tobacco is no longer employed therapeutically, but its content of " nicotine " (total alkaloids) is important in ascertaining the suitability of raw tobacco for the preparation of smoking tobacco, although this constituent is less important from this point of view than are the readiness with which the leaves burn, their aroma, content of moisture, etc. This estimation has also acquired great importance recently in view of the use of tobacco and tobacco extracts as agricultural insecticides. The Department of Agriculture of the United States of America some years ago instituted an inquiry into methods for the estimation of nicotine in tobacco, with the result that the process devised by Kissling [3] was recommended for adoption, although there are certain objections to it as regards concordance of the results obtained by different chemists using the same material. Thus, in the case of a tobacco powder, independent determination of nicotine by five chemists gave amounts varying from 0·53 to 0·81 per cent., and for the same tobacco extract percentages varying from 2·2 to 4·24.[4] The method is carried out in the following way : The finely powdered tobacco is dried at a temperature not greater than 60°, and 20 grm. of the dry material are mixed with 10 c.c. of alcoholic soda made by dissolving 6 grm. of sodium hydroxide in 40 c.c. of water and diluting to 100 c.c. with 90 per cent. alcohol. This mass is extracted in a Soxhlet

[1] *Berichte*, 1901, **34**, 696.
[2] Laiblin, *Annalen*, 1879, **196**, 130.
[3] *Zeit. Anal. Chem.* 1882, **21**, 64, 383 ; 1895, **34**, 413 ; 1896, **35**, 309, 731.
[4] *U.S. Dept. Ag. Chem. Div. Bull. No.* 101 *of* 1910.

apparatus for five hours with ether, the solvent distilled off, and the residue mixed with 50 c.c. of 0·4 per cent. soda solution and steam-distilled. The distillate is titrated with N-sulphuric acid, using cochineal or phenacetolin as indicator. In the case of tobacco extracts, 5 grm. of the extract are mixed with 10 c.c. of alcoholic soda as above, and enough ground calcium carbonate added to form a moist mass free from lumps. This is then packed in a Soxhlet apparatus and the rest of the process carried out as above.

The question has also been investigated by R. M. Chapin, who suggests an improved form of Bertrand and Javillier's process,[1] which, from the point of view of the examination of tobacco extracts, has the merit of not including in the " nicotine " pyridine bases, should these have been added to the extract. The process is equally applicable to tobacco, the alkaloids being first extracted by Kissling's method. The directions given by Chapin [2] may be summarised thus : Enough extract to contain 1 to 2 grm. of nicotine is weighed, washed into a 500 c.c. round-bottomed flask, and 1 to 1·5 grm. of solid paraffin, one or two pieces of pumice-stone, and excess of caustic soda solution added. This mixture is distilled in a current of steam and the distillate collected in 10 c.c. of dilute (1 to 4) hydrochloric acid, the flask containing the mixture being heated to keep the contents to a low volume without allowing the separation of solid matter. Distillation is continued until the distillate gives no opalescence with a drop of silicotungstic acid solution in presence of a drop of dilute hydrochloric acid, care being taken that the mixture in the flask remains strongly alkaline to the end. The distillate, which should still be acid, is diluted to a convenient known volume, thoroughly mixed, and then filtered, the first portion being rejected. An aliquot portion containing about 0·1 grm. nicotine is mixed with 3 c.c. of dilute (1 to 4) hydrochloric acid for each 100 c.c. of liquid, and 1 c.c. of a 12 per cent. solution of silicotungstic acid added for each 0·01 grm. of nicotine supposed to be present, and the mixture stirred thoroughly and set aside for eighteen hours. The precipitate should then be completely crystalline, and when stirred should settle rapidly, indicating absence of pyridine bases. It is filtered and washed with cold water containing 1 c.c. of strong hydrochloric acid per litre, until the washings give no precipitate

[1] *Bull. Sci. Pharmacol.* 1909, **16,** 7.
[2] *Bull.* 133, *Bur. Anim. Ind. U.S. Dept. Agric.* 1911.   *Cf.* Shedd, *Journ. Agric. Res.* 1923, **24,** 961.

with a dilute aqueous solution of nicotine. The wet paper and precipitate are transferred to a platinum crucible, dried at a gentle heat, then carbonised, and finally ignited, this being completed by exposure during five to ten minutes in the flame of a Teclu burner or blowpipe. The weight of the residue multiplied by 0·114 gives the weight of nicotine in the aliquot part taken for analysis. If greater accuracy is required, the nicotine silicotungstate may be collected in a Gooch crucible, washed as described, dried at 125°, and weighed ; this salt, when anhydrous, contains 10·12 per cent. of nicotine ; it is deliquescent, and the crucible containing it should be enclosed in a stoppered weighing bottle during cooling and weighing.

The principal objections to Kissling's method are that any ammonia present in tobacco and any pyridine bases added to tobacco extract are estimated as nicotine, and the more recent work on the subject deals chiefly with methods of overcoming these difficulties either by the use of various precipitants for alkaloids, such as silicotungstic acid (*see above*), arsenotungstic acid,[1] potassium mercuric iodide,[2] picric acid,[3] or iodine,[4] or by determination of the optical rotation of the distillate.[5] For a critical discussion and comparison of these methods, *see* Rasmussen.[6]

Nicotine, $C_{10}H_{14}N_2$. The alkaloid when pure is a colourless oil, b.p. 246·1°/730·5 mm. (*decomp.*), $D_4^{10°}$ 1·0180, $D_4^{20°}$ 1·00925, $[\alpha]_D^{20°}$ $-166\cdot39°$,[7] $-168\cdot5°$,[8] with a pyridine-like odour and unpleasant burning taste ; it may be distilled unchanged with steam, in hydrogen, or under reduced pressure (20 to 40 mm.). Nicotine is readily soluble in alcohol, ether or light petroleum, and miscible with water in all proportions below 60° and above 210°.[9] On addition of water, heat is evolved, and a dihydrate formed.[10] The salts are dextrorotatory, readily soluble in water, and do not crystallise easily ; the

[1] Guglialmeli and Hordh, *Anal. Soc. Quim. Argentina*, 1919, **7**, 121.

[2] Kissling, *Schweiz. Woch. Chem. Pharm.* 1911, **49,** 537 ; *see Chem. Zentr.* 1911 [ii], 1840.

[3] Spallino, *Gazzetta*, 1913, **43** [ii], 493.

[4] Harrison and Self, *Pharm. Journ.* 1912 [iv], **34,** 718.

[5] Tingle and Ferguson, *Trans. Roy. Soc. Canada*, 1916 [iii], **10,** 19 ; *cf.* Toth and Krampera, *Chem. Zeit.* 1911, **35,** 926 ; and Degrazia, *Fachl. Mitt. öst. Tabakregie*, 1910, **87,** 149.

[6] *Zeit. Anal. Chem.* 1916, **55**, 81. *Cf.* Kissling, *Chem. Zeit.* 1916, **40,** 594.

[7] Ratz, *Monats.* 1905, **26,** 1241.

[8] Jephcott, *Trans. Chem. Soc.* 1919, **115**, 105.

[9] Hudson, *Zeit. phys. Chem.* 1904, **47,** 113 ; *cf.* Jephcott, *loc. cit.*

[10] Tsakalotos, *Bull. Soc. Chim.* 1909 [iv], **5,** 397. *Cf.* Jephcott, *loc. cit.*

hydrochloride, $B.HCl$, has $[\alpha]_D + 102 \cdot 2^\circ$; the sulphate, $B_2.H_2SO_4$, $[\alpha]_D + 84 \cdot 8^\circ$; and acetate, $[\alpha]_D + 110 \cdot 29^\circ$. When aqueous solutions of nicotine hydrochloride or sulphate are heated in sealed tubes at 180°–250°, they become optically inactive.[1] The acid d-tartrate, $B.2H_2C_4H_4O_6.2H_2O$, crystallises from alcohol on addition of ether, m.p. 88°–89° (hydrated): the neutral d-tartrate, $B.H_2C_4H_4O_6.2H_2O$, similarly crystallised, has m.p. $68 \cdot 5^\circ$ (hydrated). The platinichloride is a yellow microcrystalline substance of indefinite melting point. The picrate, $B.2C_6H_2(NO_2)_3OH$, forms short prisms, m.p. 218°, and is characteristic.

Nicotine may be detected by the formation with aqueous solutions of mercuric chloride of a white crystalline precipitate, by the black precipitate formed under similar conditions with potassium platinic iodide, and the crystalline periodide, $BI_2.HI$, formed when a solution of the base in ether (1 : 100) is mixed with iodine dissolved in ether.

Constitution. The presence of a pyridine nucleus in nicotine was established by Huber,[2] Weidel,[3] and Laiblin,[4] who, using different oxidising agents, obtained from the base nicotinic acid (pyridine-2-carboxylic acid). Further evidence of this was afforded by the formation of hexahydronicotine by reduction of the base with sodium in amyl alcohol.[5] The empirical formula of nicotine may, therefore, be extended thus, $C_5H_4N.C_5H_{10}N$, and the more recent work concerns the determination of the nature of the $C_5H_{10}N$ residue. The empirical composition of this group is identical with that of piperidine, and the behaviour of nicotine in certain reactions is well explained if it be assumed to be 2-piperidyl-3-pyridine, and this view of its structure was commonly accepted until Laiblin [6] found that zinc nicotine chloride, when distilled with lime, gave a mixture of pyridine, methylamine and pyrrole ; the formation of the two latter substances from a partially reduced dipyridyl is not readily explicable. Later Blau and Herzig and Meyer observed that nicotine, heated with hydriodic acid at 300° yielded a molecule of methylamine, indicating the presence of the group, $N.CH_3$, and the dipyridyl formula was finally disposed of by Blau, who prepared 2 : 3-dipiperidyl, and showed that it was not identical with hexa-

[1] Pictet and Rotschy, *Berichte*, 1900, **33**, 2353.
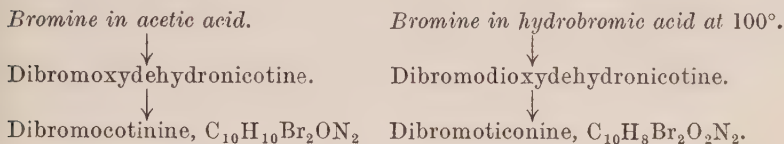[2] *Annalen*, 1867, **141**, 271.
[3] *Ibid.* 1873, **165**, 328.
[4] *Berichte*, 1877, **10**, 2136.
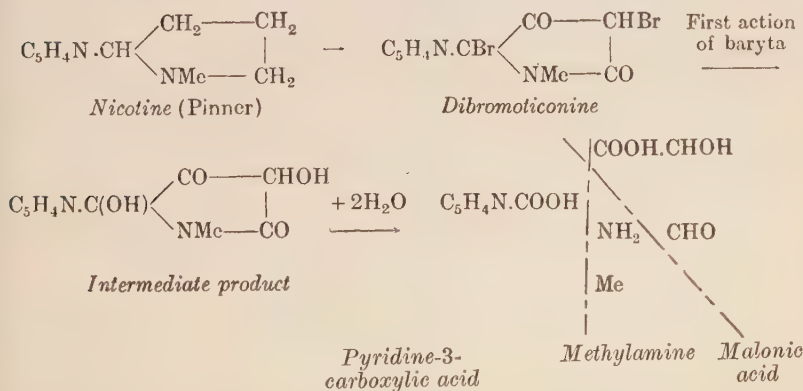[5] Liebricht, *ibid.* 1886, **19**, 2587.
[6] *Annalen*, 1879, **196**, 172.

hydronicotine.[1]   The reaction which has afforded most information regarding the structure of the $C_5H_{10}N$ residue is that of bromine on the base, investigated by Pinner.[2]   The derivatives so obtained may be grouped as follows :

Bromine in acetic acid.	*Bromine in hydrobromic acid at* 100°.
↓	↓
Dibromoxydehydronicotine.	Dibromodioxydehydronicotine.
↓	↓
Dibromocotinine, $C_{10}H_{10}Br_2ON_2$	Dibromoticonine, $C_{10}H_8Br_2O_2N_2$.

Dibromocotinine when warmed with alkalis, furnished methyl-amine, oxalic acid, and 3-methyl pyridyl ketone, $CH_3CO.C_5H_4N$, and dibromoticonine with baryta water at 100° gave methylamine, malonic acid, and pyridine-3-carboxylic acid.

These reactions can be explained on the assumption that the side-chain in nicotine consists of a series of three primary carbon atoms ending in a group, $N.CH_3$, and that since difficulty is experienced in reducing nicotine further than the hexahydro-derivative, the side-chain is closed, *i.e.*, that it is a *N*-methylpyrrolidine.   On this view of the structure of nicotine the formation of dibromoticonine and its decomposition products may be represented thus :

$$C_5H_4N.CH \Big\langle \genfrac{}{}{0pt}{}{CH_2——CH_2}{||} \Big\rangle \atop {NMe—— CH_2}$$

Nicotine (Pinner)

$$\rightarrow \quad C_5H_4N.CBr \Big\langle \genfrac{}{}{0pt}{}{CO——CHBr}{NMe——CO} \Big\rangle \quad \text{First action of baryta}$$

Dibromoticonine

$$C_5H_4N.C(OH) \Big\langle \genfrac{}{}{0pt}{}{CO——CHOH}{NMe——CO} \Big\rangle + 2H_2O$$

Intermediate product

$$\longrightarrow \quad C_5H_4N.COOH$$

Pyridine-3-carboxylic acid

COOH.CHOH

NH₂   CHO

Me

Methylamine   *Malonic acid*

Etard [3] observed that benzoyl chloride reacts with nicotine to form a benzoyl derivative which Pinner subsequently showed was derived from an isomeride of nicotine, which he named *metanicotine* (*iso-*

[1] *Berichte*, 1891, **24**, 326 ; 1893, **26**, 628, 1029.
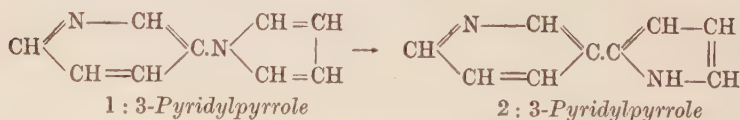[2] *Ibid.* 1892, **25**, 2816 ; 1893, **26**, 292, 769.
[3] *Compt. rend.* 1893, **117**, 170, 278.

nicotine), and whose formation he explained in the following way : [1]

$$CH_2-CH_2$$
$$C_5H_4N.CH\Big\langle \quad | \quad \rightarrow \quad C_5H_4N.CHCl.CH_2\cdot CH_2.CH_2.NMe.COC_6H_5 \rightarrow$$
$$NMe.CH_2$$

Nicotine   *Benzoyl chloride addition product*

$$C_5H_4N.CH : CH.CH_2.CH_2.NMe.CO.C_6H_5.$$
*Benzoyl*meta*nicotine*
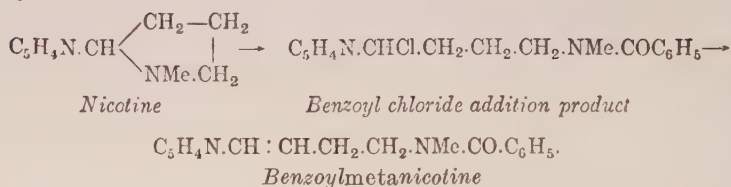
*meta*Nicotine on reduction with hydriodic acid yields an iododihydro*meta*nicotine, which with zinc dust and hydrochloric acid is converted into dihydro*meta*nicotine, and this in turn yields a *N*-bromo-derivative which, in presence of sulphuric acid, furnishes *dl*-nicotine.[2] Pinner's formula explains equally well Blau's observation [3] that nicotine furnishes on reduction both a hexahydride and an octohydride, the latter being formed by the opening and reduction of the pyrrolidine ring.   It also accounts for Pictet and Genequand's observation [4] that nicotine itself with methyl iodide forms nicotine methiodide, whilst nicotine hydriodide with this reagent gives *meta*nicotine methiodide, and that the latter on oxidation yields trigonelline (betaïne of pyridine-3-carboxylic acid ; *cf.* p. 21).

The validity of Pinner's nicotine formula has been established by the synthesis of the alkaloid, accomplished by Pictet and his co-workers.   Pictet and Crepieux [5] found that when the pyridine amide of mucic acid is distilled it yields 1 : 3-pyridylpyrrole, and this at a red heat undergoes intramolecular change, yielding 2 : 3-pyridylpyrrole thus :

$$CH\Big\langle \begin{matrix} N——CH \\ CH=CH \end{matrix} \Big\rangle C.N\Big\langle \begin{matrix} CH=CH \\ | \\ CH=CH \end{matrix} \rightarrow CH\Big\langle \begin{matrix} N——CH \\ CH=CH \end{matrix} \Big\rangle C.C\Big\langle \begin{matrix} CH—CH \\ || \\ NH—CH \end{matrix}$$

       1 : 3-*Pyridylpyrrole*   2 : 3-*Pyridylpyrrole*

The potassium derivative of the latter reacts with methyl iodide forming 1-methyl-2 : 3-pyridylpyrrolemethiodide, which is identical with nicotyrine methiodide and yields nicotyrine on distillation with lime.[6]   The latter can also be obtained by gentle oxidation of

[1] *Berichte*, 1894, **27**, 1056, 2861.
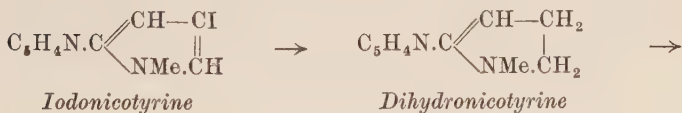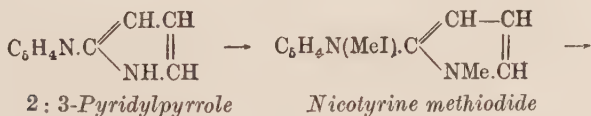[2] Löffler and Kober, *ibid.* 1909, **42**, 3431.
[3] *Ibid.* 1891, **24**, 326 ; 1893, **26**, 628, 1029.
[4] *Ibid.* 1897, **30**, 2117.
[5] *Ibid.* 1895, **28**, 1904.
[6] Pictet and Rotschy, *ibid*, 1904, **37**, 1225.

nicotine with silver oxide or potassium ferricyanide,[1] four atoms of hydrogen being removed from the pyrrolidine ring, and this change can be reversed without at the same time reducing the pyridine nucleus by the ingenious device of introducing an iodine atom by treatment with iodine in presence of alkali and reducing the iodo-nicotyrine so formed with tin and hydrochloric acid to a dihydro-nicotyrine,[2] isomeric but not identical with nicoteine (p. 59) or dehydronicotine previously prepared by Pinner and Wolffenstein.[3] This dihydronicotyrine furnished a perbromide,[4] which on reduction yielded a tetrahydronicotyrine, identical with dl-nicotine, and this by crystallisation of the dextro-ditartrate gave l-nicotine, b.p. $246°–246·5°/734·5$ mm., $D_{4°}^{10°}$ $1·0177$ and $[\alpha]_D^{20°} - 160·93°$, identical with the natural alkaloid.[5] The d-nicotine simultaneously prepared had b.p. $245·5°–246·5°/729$ mm., $D_{4°}^{10°}$ $1·0171°$, and $[\alpha]_D^{20°} + 163·17°$.

$$C_5H_4N.C\diagdown_{NH.CH}^{CH.CH} \longrightarrow C_5H_4N(MeI).C\diagdown_{NMe.CH}^{CH—CH} \longrightarrow$$

2 : 3-*Pyridylpyrrole* *Nicotyrine methiodide*

$$C_5H_4N.C\diagdown_{NMe.CH}^{CH—CI} \longrightarrow C_5H_4N.C\diagdown_{NMe.CH_2}^{CH—CH_2} \longrightarrow$$

Iodonicotyrine *Dihydronicotyrine*

$$C_5H_4N.C\diagdown_{NMeBr_2.CH_2}^{CBr—CH_2} \longrightarrow C_5H_4N.CH\diagdown_{NMe.CH_2}^{CH_2—CH_2}$$

Bromodihydronicotyrine *Tetrahydronicotyrine*
dibromide *(Nicotine)*
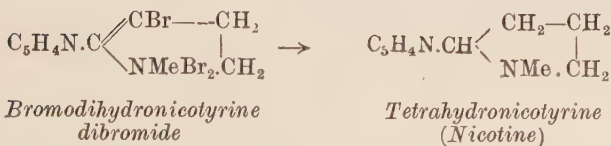
As some of the intermediate products formed in the course of this synthesis are of considerable interest, their more important constants are recorded in the following table, together with those of d-, l-, and dl-nicotine.

[1] Cahours and Etard, *Bull. Soc. Chim.* 1880 [ii], **34,** 449 ; Blau, *Berichte,* 1894, **27,** 2538.
[2] Pictet and Crepieux, *Berichte,* 1898, **31,** 2018.
[3] *Ibid.* 1895, **28,** 456.
[4] Pictet, *ibid.* 1900, **33,** 2355.
[5] Pictet and Rotschy, *ibid.* 1904, **37,** 1225.

Nicotine and Allied Bases

	Formula.	B.p. or m.p.	Density.	Picrate m.p.	Other charac-teristics.
1 : 3-Pyridylpyrrole [1]	$C_9H_8N_2$	B.p. 250°–251°/730 mm.	$1\cdot1044_{4°}^{24°}$	Needles, 178°	Platinichloride, m.p. 190° (*decomp.*)
2 : 3-Pyridylpyrrole [1]	$C_9H_8N_2$	M.p. 72°	—	Prisms, 182°	Platinichloride, m.p. 150° (*decomp.*)
Nicotyrine [2]	$C_{10}H_{10}N_2$	B.p. 280°–281°	$1\cdot124^{13°}$	Needles, 162°	Platinichloride, m.p. 158°
Dehydronicotine [3]	$C_{10}H_{12}N_2$	B.p. 265°–275°	—	Minute prisms, 208°	Platinichloride, m.p. above 260°
Dihydronicotyrine [4]	$C_{10}H_{12}N_2$	B.p. 248°/760 mm.	—	Needles, 156°	Platinichloride, m.p. above 300°
Tetrahydronicotyrine [2]	$C_{10}H_{14}N_2$	B.p. 242°–243°	$1\cdot0084_4^{20°}$	Needles, 218°	Synthetic *dl*-nicotine
dl-Nicotine [2]	$C_{10}H_{14}N_2$	B.p. 242°–243°	$1\cdot0082_{4°}^{20°}$	Needles, 218°	Racemised natural *d*-nicotine
d-Nicotine [2]	$C_{10}H_{14}N_2$	B.p. 246°/729 mm.	$1\cdot0094_{4°}^{20°}$	—	Deracemised tetrahydroni-cotyrine
l-Nicotine [2]	$C_{10}H_{14}N_2$	B.p. 246°/730 mm.	$1\cdot0097_4^{20°}$	Needles, 218°	Natural nicotine
Hexahydronicotine [5]	$C_{10}H_{20}N_2$	B.p. 244°–245°	—	Oil, becom-ing crystal-line on standing.	Platinichloride, m.p. 226°–228°
Octohydronicotine [6]	$C_{10}H_{22}N_2$	B.p. 259°–260°	—	M.p. 285°	Platinichloride, m.p. 202°
*meta*Nicotine [7]	$C_{10}H_{14}N_2$	B.p. 275°–278°	—	Needles, m.p. 114° (*hydrated*) 163° (*dry*)	Platinichloride, m.p. 255° Aurichloride, m.p. 160° (*decomp.*)

Nicotimine, $C_{10}H_{14}N_2$. This isomeride of nicotine was isolated by Pictet and Rotschy [8] from crude nicotine by treatment with nitrous acid, which converts it into the nitrosoamine from which nicotimine, still containing a little nicotine, can be regenerated by boiling with hydrochloric acid.   The alkaloid can be finally purified by conversion into the benzoyl derivative (oil, b.p. above 350°), and fractional distillation of this to remove the last traces of nicotine

[1] Pictet and Crepieux, *Berichte*, 1895, **28**, 1904.
[2] Pictet and Rotschy, *ibid.* 1904, **37**, 1225.
[3] Pinner and Wolffenstein, *ibid.* 1892, **25**, 1430.
[4] Pictet and Crepieux, *ibid.* 1898, **31**, 2018.
[5] Blau, *ibid.* 1893, **26**, 1031.
[6] *Ibid.* p. 629.
[7] Pinner, *ibid.* 1894, **27**, 1053, 2861.
[8] *Berichte,* 1901, **34**, 696.

(fraction boiling 240°–250°). Nicotimine is a colourless alkaline oil, b.p. 250°–255°, miscible with water and the usual organic solvents in all proportions. The hydrochloride is crystalline but highly deliquescent ; the platinichloride forms bright yellow minute transparent crystals and begins to decompose at 270°, the aurichloride occurs in bright yellow leaflets, which melt under water and have m.p. 182°–185° (*decomp.*) ; the mercurichloride separates from hot water in slender needles and decomposes at 190°, the picrate is precipitated as an oil and slowly solidifies to thick yellow prisms, m.p. 163°.

According to Pictet [1] nicotimine does not contain a pyrrole nucleus, and is probably represented by the following formula, which is that formerly assigned to nicotine, viz., 2-piperidyl-3-pyridine.

$$CH:CH.C\underline{\quad}CH.CH_2.CH_2$$
$$\mid \qquad \parallel \quad \mid \qquad \mid$$
$$CH:N\underline{\quad}CH\;NH.CH_2.CH_2$$
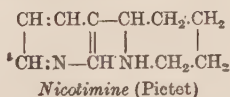
Nicotimine (Pictet)

Nicoteine, $C_{10}H_{12}N_2$. In addition to nicotine and nicotimine the tobacco extract examined by Pictet and Rotschy [2] contained two alkaloids which remained in the alkaline liquors after the first two had been removed by steam-distillation and were obtained by extraction of this first with ether, which removed nicoteine, and then with chloroform, which took out nicotelline (*see* p. 60).

Nicoteine is a colourless alkaline liquid, b.p. 266°–267°, $D_4^{12.5°}$ 1·0778, $[\alpha]_D - 46·41°$, miscible with water and most organic solvents in all proportions. The salts are lævorotatory, but much less so than the base : the hydrochloride, B.2HCl, is a gum, and has $[\alpha]_D - 8·27°$. The platinichloride, B.2HCl.PtCl$_4$, forms minute prisms and does not melt below 280° ; the aurichloride separates from warm water in tabular crystals and melts at 186° (*decomp.*) ; the picrate is precipitated as an oil and gradually changes into large yellow prisms, m.p. 165°.

Nicoteine forms a dimethiodide, is oxidised by nitric acid to nicotinic acid (pyridine-3-carboxylic acid) gives the pyrrole reaction and on treatment with silver oxide passes into its isomeride dihydronicotyrine. On these grounds Pictet has assigned to it the following formula [3] :

[1] *Arch. Pharm.* 1906, **244**, 388.
[2] *Berichte*, 1901, **34**, 700.
[3] *Arch. Pharm.* 1906, **244**, 385.

CH　　CH$_2$—CH　　　　　　　CH　　CH=CH
CH　C——CH　CH　　　　　　CH　C——CH　CH$_2$
CH　CH　　　N.CH$_3$　　　　　CH　CH　　　N.CH$_3$
　N　　　　　　　　　　　　　　　N

(I) *Nicoteine*　→　(II) *Dihydronicotyrine*
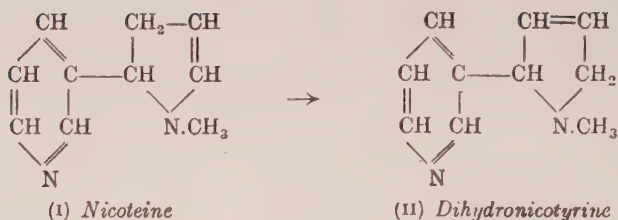
*iso***Nicoteine,** $C_{10}H_{12}N_2$. This alkaloid was obtained by Noga [1] from an extract of Turkish tobacco leaves along with nicoteine (*see* p. 59), nicotelline, and nicotoine (*see* p. 61). It is a viscous, colourless liquid, b.p. 293° (*decomp.*), $D_4^{20°}$ 1·0984, $n_D^{20°}$ 1·5749, $[\alpha]_D$ 0°, readily soluble in most organic solvents, but sparingly so in water or light petroleum. The salts crystallise well. The base forms a methiodide, yields nicotinic acid on oxidation, gives the pyrrole reaction, and decolorises permanganate. On these grounds Noga assigns to it the formula given below. There are now four distinct substances (*cf.* p. 58) all believed to be pyridyl-3-*N*-methyl-dihydropyrroles and only three possible formulæ, so that one of them must be misrepresented unless *iso*nicoteine turns out to be identical with dehydronicotine, which is not impossible.

$C_5H_4N.CH\big<{CH=CH \atop NMe—CH_2}$　$C_5H_4N.CH\big<{CH_2—CH \atop NMe—CH}$　$C_5H_4N.C\big<{CH——CH_2 \atop NMe—CH_2}$

(I) $\triangle^3$-*Dihydronicotyrine* 　(II) *Nicoteine* (Pictet) [2] 　(III) *isoNicoteine*
　(Pictet) [2] 　　　　*Dehydronicotine* (Pinner) [3] 　　(Noga)
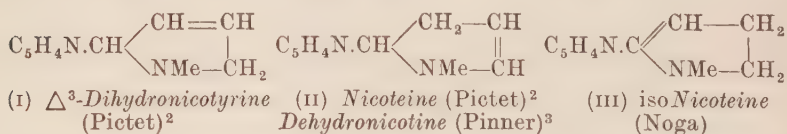
Formulæ (I) and (II) each contain an asymmetric carbon atom, and nicoteine (II) is optically active, whilst formula (I) assigned to dihydronicotyrine seems to be fairly well established. The doubtful cases seem, therefore, to be dehydronicotine and *iso*nicoteine, and the latter especially needs further investigation.

Nicotelline, $C_{10}H_8N_2$. This base, after the removal of nicoteine, is extracted from the aqueous liquid by chloroform, and on adding light petroleum to the latter, crystallises out in colourless needles, m.p. 147°–148°, b.p. above 300°; its aqueous solution is neutral to litmus. The alkaloid, unlike any of the other tobacco alkaloids, yields a sparingly soluble, crystalline dichromate. It does not

[1] *Fachl. Mitt. öst. Tabakregie*, 1914 (*Chem. Soc. Abstr.* 1915 [i], 711).
[2] *Arch. Pharm.* 1906, **244,** 385.
[3] *Berichte*, 1895, **28,** 456.

decolorise acid permanganate, and appears not to be a pyrrole derivative.[1]

Nicotoine, $C_8H_{11}N$, obtained by Noga from an extract of Turkish tobacco (*see iso*nicoteine, p. 60) is a colourless, alkaline liquid, b.p. 208°, $D_{4°}^{21°}$ 0·9545, $n_D^{20°}$ 1·5105, and is stated to yield well-crystallised salts.

Pyrrolidine, C_4H_9N, and *N*-Methylpyrroline, C_5H_9N. These simple bases were obtained by Pictet and Court [2] by the fractional distillation of crude nicotine, and are believed by them to exist as such in tobacco and not to be formed by the decomposition of the more complex bases during extraction.

Physiological Action of Tobacco Alkaloids. Nicotine is highly toxic. According to Mayor [3] the *lævo*-modification (natural nicotine) is twice as toxic as the *dextro*-form, and the physiological effects produced are also somewhat different. Nicotine affects both the central and peripheral nerves, and increases the activity of the secreting glands. It causes first a rise and then a fall in blood-pressure and induces contraction of the stomach-walls resulting in nausea and vomiting. The respiration is at first rapid and shallow, then somewhat deeper, but eventually becomes slower, and if not interrupted by convulsions gradually becomes weaker, death resulting finally from paralysis of the respiration.[4] Nicoteine appears to be somewhat more poisonous than *l*-nicotine. The use of tobacco in medicine has ceased, but in recent years nicotine has been recommended for hypodermic injection in tetanus, and the salicylate as a remedy for certain skin affections. Nicotine sulphate has also been recommended as a veterinary anthelmintic.

[1] *Arch. Pharm.* 1906, **244,** 375.
[2] *Chem. Soc. Abstr.* 1915 [i], 711.
[3] *Arch. Sci. phys. et nat.* 1904, **17,** 418.
[4] Veyrassat, *ibid.* 1889, **12,** 220.
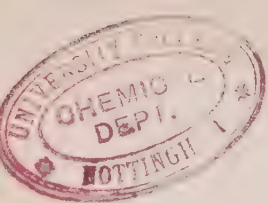
III. TROPANE GROUP

(I) SOLANACEOUS ALKALOIDS

THE term " solanaceous alkaloids " should be applied to all the alkaloids obtained from solanaceous plants, but it has long been the practice to restrict it to the following group :

> *Apoatropine* and *belladonnine*, $C_{17}H_{21}O_2N$.
> *Atropine* and *hyoscyamine*, $C_{17}H_{23}O_3N$.
> *Norhyoscyamine* and *noratropine*, $C_{16}H_{21}O_3N$.
> *Hyoscine* (*scopolamine*), $C_{17}H_{21}O_4N$.
> *Tropacocaine*, $C_{15}H_{19}O_2N$.
> *Meteloidine*, $C_{13}H_{21}O_4N$.

The members of the group present several features in common ; they are esters of tropic, atropic or tiglic acid, yielding on hydrolysis one of these acids together with a basic alcohol such as tropine, nortropine, pseudotropine, teloidine, or oscine (scopoline). Further, they give characteristic aurichlorides and picrates, which are useful in distinguishing the various members of the group. Only three of the alkaloids, atropine, hyoscyamine, and hyoscine, are used to any considerable extent in medicine. Atropine, the solanaceous alkaloid of most commercial importance, rarely, if ever, occurs as such in plants, and is generally made by racemisation of its lævo-isomeride, hyoscyamine, so that plants rich in hyoscyamine and free from the related alkaloids, *e.g.*, *Hyoscyamus muticus*,[1] form the best sources of this substance. Hyoscine is now usually obtained from *Datura Metel*. The quantities of total alkaloids found in the chief plants yielding them are given in the table on p. 63.

For the isolation of these alkaloids on a small scale for investigation, the following method is generally applicable : The finely ground material is exhausted with cold alcohol and the solvent distilled off under reduced pressure until practically the whole has been removed. In the case of oily material, such as seeds, the oil may be removed first by careful percolation with light petroleum,

[1] Dunstan and Brown, *Trans. Chem. Soc.* 1899, **75**, 72 ; and 1901. **79**, 71.

Name of plant.	Part of plant.	Total alkaloids per cent.	Constituents.	References.
Atropa Belladonna	Leaves	0·15–0·60 av. 0·40	Chiefly hyoscyamine	—
	Roots	0·1–0·7 av. 0·50	,, ,,	Old roots may contain a little atropine (Gadamer)
	Seeds	0·831	,, ,,	—
	Whole plant	0·23–1·08	,, ,,	—
Datura spp.				
D. arborea . .	Leaves	0·44	Chiefly hyoscine, some hyoscyamine in young stems and roots	Kircher, *Arch. Pharm.* 1905, **243**, 309 ; 1906, **244**, 66
	Seeds	—		
	Stems	0·23		
D. fastuosa .	Fruits	0·202	—	Andrews, *Trans. Chem. Soc.* 1911, **99**, 1876
var. *niger* .	Leaves and branches	0·119	Hyoscine alone or with hyoscyamine	
	Roots	0·101		
var. *flor cærul. plen.*	Seeds	0·254	,, ,,	Schmidt, *Arch. Pharm.* 1906, **244**, 66
var. *flor alb. plen.*	Seeds	0·223	,, ,,	
D. Metel 1 . .	Fruits	0·12	Usually chiefly hyoscine ; occasionally a little hyoscyamine or atropine	Kircher, *loc. cit.* ; Andrews, *loc. cit.* ; Schmidt, *Arch. Pharm.* 1910, **248**, 641
	Leaves	0·25–0·55		
	Roots	0·1 –0·22		
	Seeds	0·23–0·50		
D. meteloides 1 .	Whole plant	0·4	Hyoscine, 0·13 ; atropine, 0·03 ; meteloidine, 0·07	Pyman & Reynolds, *Trans. Chem. Soc.* 1908, **93**, 2077
D. quercifolia .	Leaves	0·42	Hyoscine and hyoscyamine	Kircher, *loc. cit.*
	Seeds	0·29		
D. Stramonium .	Leaves	0·2 –0·45	Chiefly hyoscyamine	Feldhaus, *Arch. Pharm.* 1905, **243**, 328
	Roots	0·21–0·25	Hyoscyamine and hyoscine	
	Seeds	0·2 –0·48	Chiefly hyoscyamine	Andrews, *loc. cit.* ; Umney, *Pharm. Journ.* 1903 [iv], **15**, 492
Duboisia myoporoides 1	Roots	—	Hyoscyamine, hyoscine	Merck, *Journ. Soc. Chem. Ind.* 1897, **16**, 515
Hyoscyamus spp.	Leaves	0·21–0·56	Hyoscyamine and hyoscine	—
H. albus . .	Roots	0·1 –0·14		
	Seeds	0·16		
H. muticus . ˛	Leaves	1·4	Hyoscyamine	Dunstan & Brown, *Trans. Chem. Soc.* 1899, **75**, 72 ; 1901, **79**, 71
	Leaves and stems	0·6	,,	
	Seeds	0·87–1·34	,,	
	Stems	0·6	,,	Gadamer, *Arch. Pharm.* 1898, **236**, 704
H. niger ˑˑ . .	Leaves	0·045–0·08	Chiefly hyoscyamine with some hyoscine and atropine	Umney, *loc. cit.*
	Roots	0·15–0·17		
	Seeds	0·06–0·10		
	Tops	0·07–0·10		
H. reticulatus .	Seeds	0·082	Hyoscyamine and possibly other alkaloids	*Bull. Imp. Inst.* 1911, **9**, 115
	Whole plant	0·116–0·240		
Scopolia carniolica (*S. atropoides*, *S. Hladnikiana*)	Rhizomes	0·43–0·51	Hyoscyamine, with hyoscine	Dunstan and Chaston, *Pharm. Journ.* 1889 [iii], **20**, 461 ; Ransom, *ibid.* p. 462
S. japonica 1 .	Leaves	0·18	Hyoscyamine	Schmidt and Henschke, *Arch. Pharm.* 1888 [iii], **26**, 185; Watanabe, *Abst. Chem. Soc.* 1911 [ii], 427

1 Carr and Reynolds (*Trans. Chem. Soc.* 1912, **101**, 946) have shown that these plants and *Mandragora vernalis* also contain norhyoscyamine (p. 83).

but care must be taken to test this percolate for alkaloids and to recover these, if present, by agitation of the petroleum percolate

with dilute acid. The semi-solid extract is shaken and warmed with several small quantities of water, and finally with 0·5 per cent. sulphuric acid until alkaloid is no longer extracted in appreciable quantities as indicated by one of the usual reagents (*see* p. 8). The mixed aqueous and acid extracts are filtered, and the filtrate shaken once with ether or chloroform to remove oil, resin, and non-alkaloidal impurities. The clarified aqueous liquid is made distinctly alkaline with ammonia and shaken out with successive portions of chloroform until all the alkaloids have passed into that solvent. The total chloroform extract is now washed once with a little water, dried over anhydrous sodium sulphate, and the solvent distilled off, finally under reduced pressure. The residue obtained is usually gummy, and when hyoscyamine is the predominant constituent, as in *Hyoscyamus muticus*, this residue, on solution in chloroform and addition of a few drops of light petroleum, yields crystals of hyoscyamine. In any case, by dissolving the residue in a slight excess of dilute sulphuric acid, filtering and shaking out once with ether, small further quantities of impurities are removed. On adding to this liquid ammonia solution in slight excess and shaking out several times with ether and then with chloroform, a partial separation of the alkaloids is effected ; for final separation and purification, recourse must be had to the preparation of salts, of which the oxalates, hydrobromides, and eventually the aurichlorides are the most useful. Thus two portions obtained by successive extraction with ether and chloroform may be dissolved separately in a slight excess of dilute hydrochloric acid, the aurichlorides precipitated in fractions by adding gold chloride, and recrystallised from hot water containing a little hydrochloric acid until fractions of constant melting-point are obtained. Atropine aurichloride separates as an oil, but becomes crystalline on standing and after recrystallisation melts at 137°–139°. Hyoscyamine aurichloride is usually precipitated in crystalline form, and when pure melts at 165°. Hyoscine aurichloride is also precipitated as a rule in crystals, and when recrystallised till pure, melts at 208°.[1]

ESTIMATION OF THE TOTAL ALKALOIDS OF SOLANACEOUS PLANTS.

As already indicated, the solanaceous plants yielding hyoscyamine and hyoscine are of great importance as drugs, or as sources of

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[1] For further information on the isolation, purification, and identification of these alkaloids, *see* Dunstan and Chaston, *Pharm. Journ.* 1889 [iii], **20**, 461 ; Dunstan and Brown, *Trans. Chem. Soc.* 1899, **75**, 72 ; 1901, **79**, 71 ; Pyman and Reynolds, *ibid.* 1908, **93**, 2077 ; Andrews, *ibid.* 1911, **99**, 1871 ; Carr and Reynolds, *ibid.* 1912, **101**, 957.

PLATE I.

Fig. 1.—Belladonna leaves and flowers.   Reduced.   (Greenish.)

Fig. 2.—Henbane (*H. niger*).   Flowering top.   Reduced.   (Greenish.)

atropine and the other alkaloids of this group. Certain of them are recognised in the various national pharmacopœias, and in most cases the drugs are required to conform with certain standards, and official galenical preparations made from them are " standardised," *i.e.*, at certain stages in their manufacture the preparations are assayed for alkaloids by prescribed processes, and then concentrated or diluted to the required alkailodal content.

The crude drugs of this class recognised in the United States Pharmacopœia (9th Revision) are henbane leaves (*Hyoscyamus niger*), belladonna leaves and roots (*Atropa Belladonna*), and stramonium leaves (*Datura Stramonium*). The British Pharmacopœia, 1914, adds to these the seeds and leaves of *Datura fastuosa*. The following processes devised by Dunstan and Ransom,[1] and subsequently slightly modified,[2] are suitable for most solanaceous plants containing alkaloids of this group.

Roots. Twenty grammes of the finely ground roots are exhausted in a Soxhlet extractor with a mixture of chloroform and dry alcohol in equal parts. The solution is shaken with water (25 c.c.), when the alkaloidal salts pass into the water, which is run into a second separator. The agitation with water (25 c.c.) is repeated, and the separated aqueous liquid added to the first quantity. The 50 c.c. of aqueous solution are shaken once with a little chloroform and the latter discarded. Ammonia solution in slight excess is now added, and the liberated alkaloids extracted by shaking with several portions of chloroform, each portion after use being run into a tared flask. From the combined chloroform liquors the solvent is distilled off and the residue dried at 100° and weighed.

Leaves, Stems, Fruit Capsules, Fruits, or Seeds. Twenty grammes of the finely powdered material are exhausted by dry alcohol in a Soxhlet extractor and the solvent distilled off under reduced pressure, leaving a semi-solid residue. The latter is washed several times with small quantities of warm water, and finally with dilute (0·1 per cent.) sulphuric acid, the aqueous and acid washings are filtered into a separating funnel and washed with ether to remove non-alkaloidal impurities. The acid liquid is then rendered slightly alkaline with ammonia solution, and the alkaloids extracted by shaking several times with chloroform. The total chloroform solution is washed with a little water, dried over anhydrous sodium

[1] *Pharm. Journ.* 1883–84 [iii], **14,** 623; 1885 [iii], **16,** 237, 238, 777.
[2] Dunstan and Brown, *Trans. Chem. Soc.* 1899, **75,** 72; 1901, **79,** 71; Andrews, *ibid.* 1911, **99,** 1871.

sulphate, the solvent distilled off, and the residue dried at 100° and weighed.

Pharmacopœial Methods. The British Pharmacopœia, 1914, prescribes the following method for belladonna leaves, which are required to contain not less than 0·3 per cent. of total alkaloids. Ten grammes of the leaves in No. 60 powder are packed in a stoppered glass percolator, plugged with cotton wool, and provided with a glass tap and well shaken with 50 c.c. of a mixture of chloroform (1 volume) and ether (4 volumes), then set aside ten minutes, after which 2 c.c. of ammonia solution (sp. gr. 0·959) diluted with 3 c.c. of water are added, and the whole solution shaken frequently during one hour. The liquid is then allowed to percolate slowly and completely into a separator containing 6 c.c. of N-sulphuric acid diluted with 20 c.c. of water, and the percolation continued with 50 c.c. or more of the chloroform-ether mixture, added in small quantities, to exhaust the drug. The separator is shaken well, the acid liquid drawn off and the extraction of the alkaloids continued with two further portions (10 c.c.) of the diluted acid. The combined acid liquids are now made alkaline with ammonia solution, and the liberated alkaloids extracted by shaking with three successive portions (15, 15, 5 c.c.) of chloroform. The total chloroform solution is evaporated to dryness, the residue dissolved in 3 c.c. of ether, the solution again evaporated to dryness, the residual alkaloids dissolved in 10 c.c. of $N/20$ sulphuric acid and titrated with $N/20$ sodium hydroxide, using tincture of cochineal as indicator. If x is the number of cubic centimetres of $N/20$ sodium hydroxide used, the percentage of alkaloids in the leaves is given by the formula $(10 - x) \times 0.1446$.

The Pharmacopœia of the United States (9th Revision) prescribes the following method of assay for solanaceous drugs. The example quoted is for belladonna root and the variations specified for other drugs are indicated in footnotes.

Fifteen grammes [1] of belladonna root in No. 60 powder are placed in a 250 c.c. flask with 150 c.c. of a mixture of chloroform (1 volume) and ether (2 volumes), shaken well and set aside for ten minutes. Five cubic centimetres of ammonia solution (sp. gr. 0·958 at 25° C.) are then added and the flask shaken vigorously at intervals of ten minutes during two hours, after which 15 c.c.[2] of water are added,

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[1] In the case of henbane leaves, 30 grm. are used, with 300 c.c. of the chloroform-ether mixture in a 500 c.c. flask.

[2] For belladonna and stramonium leaves 25 c.c. of water are added, and for henbane 40 c.c.

the flask again shaken and 100 c.c.[1] (= 10 grm. of the drug) decanted, through cotton wool into a separator, the flask and cotton wool being rinsed with a little ether, which is added to the decanted liquor. The alkaloids are then completely extracted by agitation with weak sulphuric acid. The collected acid washings are then made alkaline to litmus with ammonia and the alkaloid completely extracted with chloroform. The chloroform solution is evaporated to dryness,[2] the residue dissolved in 5 c.c. of $N/10$ sulphuric acid, and the excess titrated back with $N/50$ potassium hydroxide solution, using cochineal solution as indicator. Each cubic centimetre of acid used corresponds to 0·0289 grm. of alkaloids. The root is required to contain at least 0·45 per cent.[3]

Both Pharmacopœias prescribe methods of assay for galenical preparations of these drugs, based on those summarised above, but with variations, chiefly in the preliminary manipulation, to suit the particular preparation.

Atropine, $C_{17}H_{23}O_3N$. It is probable that this alkaloid does not occur in more than traces in solanaceous plants, and its preparation by Mein [4] and by Geiger and Hesse [5] was probably due to the fact that the hyoscyamine originally present in the plant was converted into atropine in the process of extraction. Liebig assigned to it its present formula, and it was later shown by von Planta [6] to be identical with daturine, obtained from stramonium. Commercially the alkaloid is obtained by treating crude hyoscyamine, extracted from the plants by a process identical in principle with that already described (p. 62), with dilute alkali, when it undergoes isomerisation to atropine.[7] The racemic base may then be purified by conversion into and re-crystallisation of the oxalate.

The alkaloid crystallises from alcohol on addition of water or from chloroform on addition of light petroleum, in colourless, elongated prisms, m.p. 118°, sublimes unchanged when heated rapidly, is readily soluble in alcohol (1 in 1·46 at 25°) or chloroform

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[1] In the case of henbane 200 c.c. (= 20 grm. of the drug) are decanted.

[2] For belladonna, stramonium and henbane leaves, the residue is dissolved twice in 5 c.c. of ether and evaporated to dryness each time, and only then dissolved in the acid for titration.

[3] Belladonna leaves are required to contain 0·3 per cent., henbane 0·065 per cent. and stramonium 0·25 per cent.

[4] *Annalen*, 1833, **6,** 67.

[5] *Ibid.* 1833, **5,** 43 ; **6,** 44 ; **7,** 269.

[6] *Arch. Pharm.* 1850, **74,** 245. *cf.* Pesci, *Gazzetta*, 1882, **12,** 59.

[7] Will and Bredig, *Berichte*, 1888, **21,** 2797 ; *cf.* Gadamer, *Arch. Pharm.* 1901, **239,** 294.

(1 in 1·56 at 25°), less soluble in ether (1 in 16·6 at 25°), or hot water
(1 in 86·7 at 80°), sparingly so in cold water (1 in 450 at 25°), and
almost insoluble in light petroleum.　The aqueous solution is bitter
to the taste and alkaline to litmus and phenolphthalein.　Atropine
is optically inactive when pure, but the commercial alkaloid is often
slightly lævorotatory, owing to the presence of hyoscyamine.

Atropine causes dilatation of the pupil of the eye like other
alkaloids of this group ; hence the term " mydriatic alkaloids."
A drop or two of an aqueous solution, containing 1 part of atropine
in 130,000 parts of water, when introduced into the eye of a cat is
sufficient to produce this effect.　This property may be used for the
detection of atropine, but the test should be applied with great care.
When warmed with sulphuric acid and a small crystal of potassium
dichromate, atropine develops a bitter almond odour.　Evaporated
to dryness on the water-bath with concentrated nitric acid, it gives
a residue which becomes violet on adding a drop of sodium hydroxide
in alcohol.　Atropine does not form a mercurichloride, but with a
solution of mercuric chloride gives a yellow to red precipitate of
mercuric oxide.

The salts of atropine are mostly crystalline and soluble in water.
The sulphate, $B_2.H_2SO_4.H_2O$, occurs in commerce as a colourless
crystalline powder, m.p. 194°, when dried at 100°, soluble in water
(1 in 0·38) or alcohol (1 in 3·7), and sparingly so in chloroform
(1 in 620) or ether (1 in 2,140), in each case at 25°.　It is conveniently
recrystallised by adding acetone to its solution in alcohol.　This
salt is that usually employed in medicine.　The hydrobromide,
$B.HBr$, m.p. 163°-164°, crystallises in slender needles, and the
oxalate, $B_2.H_2C_2O_4$, forms opaque warty masses of minute prisms,
m.p. 198°.　The platinichloride, $B_2.H_2PtCl_6$, is readily soluble in
dilute hydrochloric acid, and consequently is not precipitated when
atropine hydrochloride is added to platinic chloride solution con-
taining free hydrochloric acid.　On evaporation it is obtained in
monoclinic crystals, m.p. 207°-208°.　The aurichloride, $B.HAuCl_4$,
separates as an oil but solidifies to a crystalline mass, which may
be recrystallised from water containing hydrochloric acid.　The
crystals melt at 137°-139° or below 100° when heated under water.
This salt and the picrate, rectangular plates, m.p. 175°-176°, are
well adapted for the identification of the alkaloid, since the auri-
chlorides and picrates of the other alkaloids of this group crystallise
differently and melt at different temperatures.

The constitution of atropine is discussed later (p. 71).

Apoatropine (*Atropamine*), $C_{17}H_{21}O_2N$. This anhydride of atropine was first obtained by Pesci,[1] and was subsequently prepared by Merck,[2] Hesse,[3] and others, by the action of dehydrating agents upon atropine or hyoscyamine. It was also isolated under the name atropamine by Hesse [4] from belladonna root, the identity of the two being established by Merck.[2] Apoatropine crystallises from ether in prisms, m.p. 60°; it is slightly soluble in water, but readily dissolves in other ordinary solvents except light petroleum. The salts crystallise well, the hydrochloride in thin plates, m.p. 237°, and the aurichloride in needles, m.p. 110°. The base and its salts are optically inactive and are not mydriatic. When apoatropine is heated alone, or evaporated with moderately strong hydrochloric acid, it partly passes into the isomeric belladonnine (*see below*), and is partly decomposed into tropine (p. 72) and atropic acid (p. 72). A partial synthesis of apoatropine was effected by Ladenburg [5] by the esterification of tropine with atropic acid. Apoatropine is, therefore, atropyltropëine (*see* p. 73).

Belladonnine, $C_{17}H_{21}O_2N$. This isomeride of apoatropine, obtained by Hübschmann [6] from henbane berries, was examined by Kraut and later by Merling,[7] who assigned to it the formula given above, which was confirmed by Hesse,[8] who also found that on heating at 120°–130° hyoscyamine passes into atropine, then into apoatropine, and finally into belladonnine. The same author states that on heating apoatropine with hydrochloric acid at 85°–100° during eight hours in sealed tubes, belladonnine and some tropine are formed; whilst on heating at 140° during sixteen hours, bellatropine, $C_8H_{15}ON$, colourless prisms, is produced. Hesse, therefore, regards belladonnine as produced by isomerisation of the tropine portion of the apoatropine molecule, the tropine residue being converted into the isomeric bellatropine, so that on this view belladonnine is atropylbellatropëine.

Belladonnine is described as an uncrystallisable resinous base insoluble in water, but easily soluble in alcohol, ether, or chloroform: the platinichloride, m.p. 229°, and the aurichloride, m.p. 120°, are

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[1] *Gazzetta*, 1881, **11**, 538; 1882, **12**, 60.
[2] *Arch. Pharm.* 1891, **229**, 134; 1893, **231**, 110.
[3] *Annalen*, 1892, **271**, 124; 1893, **277**, 290.
[4] *Ibid.* 1891, **261**, 87.
[5] *Ibid.* 1883, **217**, 102.
[6] *Jahresberichte*, 1858, p. 376.
[7] *Berichte*, 1884, **17**, 381.
[8] *Annalen*, 1891, **261**, 87; 1892, **271**, 123; 1893, **277**, 295.

both amorphous. It is questionable whether belladonnine is a chemical individual.

Hyoscyamine, $C_{17}H_{23}O_3N$. This, the most commonly occurring alkaloid of the group is the chief alkaloidal constituent of *Atropa Belladonna, Datura Stramonium, Hyoscyamus* spp., etc. (*see* table, p. 63). The best source is *Hyoscyamus muticus.* It was obtained by Geiger and Hesse [1] from henbane, and its hydrolysis into a base and an acid was observed by Höhn and Reichardt.[2] The formula now accepted for it is due to Ladenburg,[3] who also showed that it was a physical isomeride of atropine.

Hyoscyamine crystallises from dilute alcohol in long silky needles, m.p. 108·5°, and is lævorotatory in solution, $[\alpha]_D - 22°$ in 50 per cent. alcohol [4] ; it is readily soluble in benzene, chloroform or alcohol, less so in ether or cold water.

The ordinary salts of hyoscyamine are crystalline. The sulphate, $B_2.H_2SO_4.2H_2O$, m.p. 206° (*dry*), crystallises in needles from alcohol, is bitter to the taste, neutral, and readily soluble in water. The hydrobromide, B.HBr, m.p. 151·8°, forms prisms ; both these salts are deliquescent. The aurichloride, $B.HAuCl_4$, m.p. 165°, crystallises in golden-yellow, hexagonal plates from dilute hydrochloric acid ; unlike atropine aurichloride, it does not melt when heated under water. This salt is less soluble in water containing hydrochloric acid than atropine aurichloride, from which it may be separated by fractional crystallisation. The platinichloride, m.p. 206°, is somewhat soluble in dilute hydrochloric acid, and is obtained by spontaneous evaporation of solutions of hyoscyamine hydrochloride and platinic chloride ; it forms orange-coloured prisms. The picrate, m.p. 165°, crystallises in plates.

Hyoscyamine is readily converted into the racemic modification, atropine, by melting or by the addition of small quantities of caustic alkali to its cold alcoholic solution, and this latter method is that generally employed in the manufacture of atropine from hyoscyamine. The same change is brought about by sodium carbonate or ammonia.[5]

When heated with acids or alkalis, hyoscyamine undergoes

[1] *Annalen,* 1833, **7,** 270.

[2] *Ibid.* 1871, **157,** 98.

[3] *Ibid.* 1880, **206,** 282.

[4] Carr and Reynolds, *Trans. Chem. Soc.* 1910, **97,** 1329.

[5] Will, *Berichte,* 1888, **21,** 1717 ; Will and Bredig, *ibid.* p. 2797 ; Schmidt, *ibid.* p. 1829 ; and Gadamer, *Arch. Pharm.* 1901, **239,** 294. For suggestions as to mechanism of racemisation, *see* Gadamer, *J. pr. Chem.* 1913 [ii], **87,** 312, and Frankland, *Trans. Chem. Soc.* 1913, **103,** 722.

hydrolysis into tropine and tropic acid. It is probable that the hyoscyamine is in the first place converted by these reagents into atropine, and that it is really this alkaloid which is hydrolysed. According to Gadamer,[1] when hyoscyamine is hydrolysed with cold water the products are inactive tropine and lævorotatory tropic acid. Ladenburg and Hundt [2] found that by esterification of *inactive* tropine with *lævo*tropic acid a " *l*-atropine," not identical with hyoscyamine was produced, but Amenomiya [3] has shown that Ladenburg and Hundt's *d*- and *l*-atropines were probably mixtures of atropine with *d*- and *l*-hyoscyamines. He separated *dl*-tropic acid into the *d*- and *l*- forms by crystallisation of the quinine salts, and then esterified these with tropine in 5 per cent. hydrochloric acid, and in this way obtained *d*- and *l*-hyoscyamines, the latter identical with the natural alkaloid. *d*- and *l*-Hyoscyamines have also been obtained by Barrowcliff and Tutin [4] by the deracemisation of atropine by means of *d*-camphorsulphonic acid.

CONSTITUTION OF ATROPINE AND HYOSCYAMINE

Atropine is readily hydrolysed by warming with alkalis, dilute acids or even with water.[5] By heating it with concentrated hydrochloric acid at 130° in a closed vessel, or with baryta water at 60°, it is completely resolved into tropine and tropic acid,[6] thus :

$$C_{17}H_{23}O_3N + H_2O = C_8H_{15}ON + C_9H_{10}O_3$$
$$\textit{Atropine} \qquad \textit{Tropine} \quad \textit{Tropic acid}$$
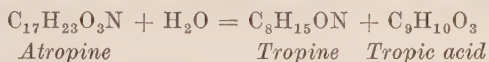
At higher temperatures the tropic acid first produced loses water and becomes atropic acid, $C_9H_8O_2$.

TROPIC ACID. The constitutions of tropic and atropic acids are known from the syntheses effected by Ladenburg and his collaborators [7] from acetophenone. The ketone (I) by treatment with phosphorus pentachloride, was converted into α-dichloroethylbenzene (II), and this, by the action of potassium cyanide in alcohol, into ethoxycyanoethylbenzene (III), which on hydrolysis yielded

[1] Will, *Berichte*, 1888, **21**, 1717; Will and Bredig, *ibid*. p. 2797; Schmidt, *ibid*. p. 1829; and Gadamer, *Arch. Pharm.* 1901, **239**, 294. For suggestions as to mechanism of racemisation, *see* Gadamer, *J. pr. Chem.* 1913 [ii], **87**, 312, and Frankland, *Trans. Chem. Soc.* 1913, **103**, 722.

[2] *Berichte*, 1889, **22**, 2590.

[3] *Arch. Pharm.* 1902, **240**, 498.

[4] *Trans. Chem. Soc.* 1909, **95**, 1969.

[5] Gadamer, *Arch. Pharm.* 1901, **239**, 294.

[6] Kraut, *Annalen*, 1863, **128**, 280 ; 1865, **133**, 87 ; 1868, **148**, 236 ; Lossen, *ibid.* 1864, **131**, 43 ; 1866, **138**, 230.

[7] *Berichte*, 1880, **13**, 376, 2041 ; 1889, **22**, 2590.

ethylatrolactic acid (IV). The latter was converted by strong hydrochloric acid into atropic acid (V), and this in turn on addition of hypochlorous acid gave chlorotropic acid (VI), which on reduction with zinc dust and iron filings in alkaline solution passed into tropic acid (VII). This series of changes may be represented thus :

(I) $Ph.CO.Me \rightarrow$ (II) $Ph.CCl_2.Me \rightarrow$ (III) $Ph.(CN)C(OC_2H_5).Me \rightarrow$
(IV) $Ph.(COOH)C(OC_2H_5).Me \rightarrow$ (V) $Ph.(COOH)C:CH_2 \rightarrow$
(VI) $Ph.(COOH)CCl.CH_2OH \rightarrow$ (VII) $Ph.(COOH)CH.CH_2OH$
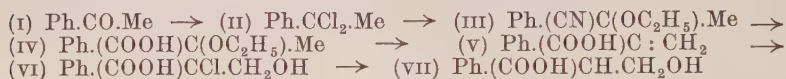
Since then other syntheses of tropic acid have been accomplished by Spiegel,[1] Müller,[2] and Wislicenus and Bilhüber.[3] Of these the most interesting is the reduction of ethyl formylphenylacetate (VIII) in moist ethereal solution by aluminium amalgam to ethyl tropate (IX) from which the acid (X) is obtainable by hydrolysis with baryta.

(VIII) $CHO.CHPh.COOC_2H_5 \rightarrow$ (IX) $HO.CH_2.CHPh.COOC_2H_5 \rightarrow$
(X) $HO.CH_2.CHPh.COOH$
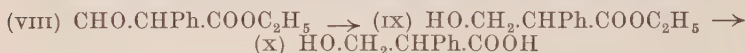
Mackenzie and Wood,[4] however, obtained low yields by this method and recommended instead the hydrolysis of acetophenone-cyanohydrin (XI) into atrolactic acid (XII), conversion of the latter by distillation under reduced pressure into atropic acid (XIII), which was then treated in ethereal solution with hydrochloric acid, and the halogen in the resulting β-chlorohydratropic acid (XIV) replaced by hydroxyl by boiling the acid with aqueous sodium carbonate solution giving tropic acid (XV) thus :

(XI) $Ph.(OH)C(CN).Me \rightarrow$ (XII) $Ph.(OH)C(COOH).Me \rightarrow$
(XIII) $Ph.C(COOH):CH_2 \rightarrow$ (XIV) $Ph.CH(COOH).CH_2Cl \rightarrow$
(XV) $Ph.CH(COOH).CH_2OH$
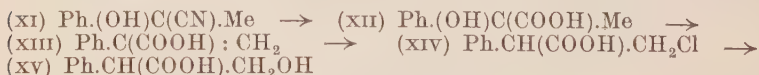
Tropic acid crystallises in prisms and melts at 117°. It contains an asymmetric carbon atom and can be resolved into d- and l-forms, which, according to King,[5] melt at 128°–129°, and have $[\alpha]_D + 81\cdot6°$ and $- 81\cdot2°$ (in water) respectively : in alcohol the specific rotation of the d-form is $+ 71\cdot8°$.

TROPINE, $C_8H_{15}ON$. This base, which is produced by the hydrolysis of several of the solanaceous alkaloids, forms rhombic tablets, m.p. 63°, b.p. 233°, soluble in water, ether, alcohol, or benzene, and is best crystallised from toluene by addition of light petroleum. It

[1] *Berichte*, 1881, **14**, 235.
[2] *Ibid.* 1918, **51**, 252.
[3] *Ibid.* p. 1237. *Cf.* von Braun, *ibid.* 1920, **53B**, 1409.
[4] *Trans. Chem. Soc.* 1919, **115**, 828.
[5] *Ibid.* 1919, **115**, 490. *Cf.* Ladenburg and Hundt, *Berichte*, 1889, **22**, 2591 ; Gadamer, *Arch. Pharm.* 1892, **230**, 207 ; Amenomiya, *ibid.* 1902, **240**, 501.

is optically inactive and has so far not been resolved into active components. Its aqueous solution is strongly alkaline, and readily absorbs carbon dioxide from the air. The salts crystallise well, the hydrochloride in plates, the picrate in yellow needles from water. The aurichloride forms golden-yellow plates, m.p. 210° (*decomp.*), and the platinichloride orange-coloured monoclinic needles, m.p. 198° (*decomp.*).

The base contains a hydroxyl group and readily undergoes esterification with acids. The esters so formed are, after the suggestion of Ladenburg, called tropëines. A considerable number of these have been made,[1] and a few of them have found application in medicine as substitutes for atropine. The following are the more important :

Tropyltropëines, $C_{17}H_{23}O_3N$. Three of these have been prepared by the combination respectively of *dl-*, *d-*, and *l*-tropic acids with tropine ; the first is identical with atropine, the two latter are the *d*- and *l*-hyoscyamines, prepared by Amenomiya (*see* p. 71).

Atrolactyltropëine (*pseudo*atropine), α-hydroxy-α-phenylpropionyltropëine, $C_{17}H_{23}O_3N$. Considerable interest attaches to this substance since atrolactic acid is isomeric with tropic acid. It forms brilliant needles, m.p. 119°.

α-Hydroxy-β-phenylpropionyltropëine, $C_{17}H_{23}O_3N$, also isomeric with atropine, crystallises in rosettes of needles, m.p. 89°–90°.

Atroglyceryltropëine, $C_{17}H_{23}O_4N$, crystallises in rectangular oblong plates, m.p. 124°–125°.

All these show well-marked mydriatic action.

Phenylglycollyltropëine (*Homatropine*), $C_{16}H_{21}O_3N$. This is the most important of the artificial tropëines, and is largely used as a substitute for atropine. It crystallises in transparent prisms, m.p. 95·5°–98·5°. The hydrobromide, colourless crystalline powder, m.p. 217°–218°, the hydrochloride, m.p. 224°–225°, and the salicylate are used in medicine. They are freely soluble in water. The aurichloride, $B . HAuCl_4$, forms prisms, and is sparingly soluble in water. Homatropine is a powerful mydriatic, and its effect is more rapid and transient than that of atropine.

It is distinguished from atropine by not giving a violet coloration on treatment with nitric acid, followed by alcoholic potassium hydroxide.

[1] *See especially* Jowett and Pyman, *Trans. Chem. Soc.* 1909, **95,** 1020 ; Jowett, Pyman and Dale, *Seventh Internat. Cong. Applied Chem.* 1909, IV. A, 1335 ; and Pyman, *Trans. Chem Soc.* 1917, **111,** 1104.

Constitution of Tropine, $C_8H_{15}ON$.   It is not possible within
reasonable limits to give an exhaustive historical account of the
investigations, which have provided our present knowledge of the
constitution of tropine ; attention will, therefore, be chiefly directed
to those reactions which form the basis upon which the now generally
accepted formula of Willstätter rests.

Tropine readily suffers dehydration by the action of strong
sulphuric or hydrochloric acid, forming a new tertiary base, TRO-
PIDINE,[1] $C_8H_{13}N$, an oily, alkaline liquid, b.p. 162°, having a coniine-
like odour.   Tropidine methiodide when heated with potassium
hydroxide yields TROPILENE, $C_7H_{10}O$ (*cf.* p. 78), and dimethylamine,
the latter affording evidence of the existence of the group : $N.CH_3$
in tropidine, and, consequently, in tropine.   By the action of bro-
mine on tropidine, Ladenburg[1] found that two substances were
produced, viz., methyldibromopyridine and 3 : 5-dibromopyridine.
When hydriodic acid reacts with tropine at temperatures above 150°,
tropidine results by the loss of a molecule of water, but at lower
temperatures an intermediate iodo-compound, $C_8H_{14}NI.HI$, is
formed, which is the hydriodide of a base in which an atom of iodine
replaces the —OH group of tropine ; by the reduction of this sub-
stance with nascent hydrogen, dihydrotropidine, $C_8H_{15}N$, results,
which cannot be obtained by direct reduction of tropidine.   This
reduced product is of interest, since its hydrochloride, on distillation,
loses a molecule of methyl chloride and gives rise to *nordihydro-*
tropidine, $C_7H_{13}N$, and this in turn furnishes 2-ethylpyridine by
distillation with zinc dust.[1]

The results so far recorded are those upon which Ladenburg
chiefly framed his formulæ representing tropine and tropidine as
N-methyl-Δ^2-tetrahydropyridines, substituted in position 2 by the
residues $.CH_2.CH_2OH$ (or $.CHOH.CH_3$) and $.CH : CH_2$ respectively
thus :

$$C_5H_7NMe.CH_2.CH_2OH \text{ or } C_5H_7NMe.CHOH.CH_3 \quad C_5H_7NMe.CH : CH_2$$
<div style="text-align:center">*Tropine*   *Tropidine*</div>
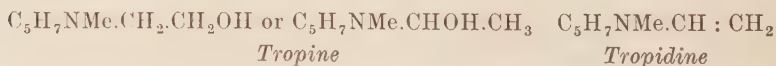
The inadequacy of these formulæ became evident when the
oxidation of tropine was studied.   When treated with potassium
permanganate, in presence of acid, or with chromic acid, tropine and
tropidine give rise to a series of oxidation products, the interrelation-
ships of which are shown in the following scheme.

[1] Ladenburg, *Annalen*, 1883, **217**, 117 ; *Berichte*, 1887, **20**, 1647.

Tropine, $C_8H_{15}ON$—by action of H_2SO_4——

Oxidation by chromic acid Oxidation by potassium permanganate

Tropinone, $C_8H_{13}ON$ *Tropigenine*, $C_7H_{13}ON$

i-*Tropinic acid*, $C_8H_{13}O_4N$ Oxidation by chromic acid

nor*Tropinone*, $C_7H_{11}ON$ *Tropidine*, $C_8H_{13}N$

Oxidation by potassium permanganate

Dihydroxytropidine, $C_8H_{13}O_2N$

By action of methyl iodide   Oxidation by chromic acid

Tropidine methiodide   i-*Tropinic acid*, $C_8H_{13}O_4N$

By action of potassium hydroxide   By " exhaustive methylation "

Tropilene, $C_7H_{10}O$ *Tropilidene*, C_7H_8, and *trimethylamine*

The most important of these products are the following :

Tropinone, $C_8H_{13}ON$. This substance, first prepared by Will-stätter,[1] crystallises on long standing in spear-shaped needles, m.p. 41°, b.p. 219°–220° under 714 mm. pressure, dissolves in the ordinary solvents, and is a strong base, liberating ammonia from its salts. It has the properties of a ketone, giving an oxime, m.p. 111°, and a semicarbazone, m.p. 212°. It is a tertiary base and the methiodide reacts violently with potassium hydroxide, producing dimethylamine and a substance which Merling regarded as a dihydrobenzaldehyde.[2] When reduced by sodium amalgam, tropinone forms, not tropine, but *pseudo*tropine, identical with that obtained by the hydrolysis of benzoyl*pseudo*tropine (*tropacocaine*), occurring naturally in coca leaves (p. 108). When reduced electrolytically or by zinc dust in hydriodic acid, a mixture of tropine and *pseudo*tropine is produced, which can be separated by fractional precipitation of the picrates, tropine picrate being the less soluble. It is possible in this way to

[1] *Berichte*. 1896, **29,** 396.
[2] *Cf.* Willstätter, *Berichte*, 1898, **31,** 1548.

convert *pseudo*tropine into tropine by oxidising to tropinone and then reducing.[1]

i-*Tropinic acid*, $C_8H_{13}O_4N$. This oxidation product of tropine and its derivatives, as well as of pseudotropine, is a substance of great importance in this group, and its constitution and relation to tropine have given rise to much discussion.[2] It crystallises in small needles, m.p. 248° (*decomp.*), is soluble in water, and almost insoluble in other media. It is a dibasic acid and yields salts, which are usually well crystallised, both with bases and acids. The formation of this dibasic acid by the oxidation of tropine is not explicable in any simple manner by Ladenburg's formula for tropine, and it was this difficulty which led Merling to propose his formula for this base (p. 77). By crystallisation of the cinchonine salt, *i*-tropinic acid can be resolved into the *d*- and *l*-forms. The first of these is produced by the oxidation of *d*- or *l*-ecgonine (p. 103).

Tropigenine, $C_7H_{13}ON$. This product of the action of potassium permanganate on tropine is a strong base, which crystallises from ether in colourless needles, m.p. 161°. It sublimes when heated to 100° *in vacuo*, absorbs carbon dioxide from the air, and is liberated from solutions of its hydrochloride by silver oxide, but not by caustic soda. Its relation to tropine is established by the fact that it is a secondary base giving a nitroso-derivative, and that it combines with methyl iodide to form tropine methiodide, showing that in its formation from tropine the methyl group attached to the nitrogen atom is replaced by hydrogen.[3]

Nortropinone, $C_7H_{11}ON$. This base results from the action of chromic acid on tropigenine and bears the same relation to the latter as tropinone does to tropine.[4] It crystallises in long, thin, deliquescent needles, m.p. 69°, is readily soluble in water or alcohol, and less so in ether. On reduction with sodium amalgam, it forms *pseudo*tropigenine, which corresponds with *pseudo*tropine. It furnishes an oxime, microscopic leaflets, m.p. 181°, and as a secondary amine, forms a nitroso-derivative, crystallising in needles, m.p. 121°.

The formation of these oxidation products, and, in particular, of the dibasic tropinic acid, led Merling[5] to represent tropine as a

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[1] Willstätter and Iglauer, *Berichte*, 1900, **33**, 1170. *Cf.* Ger. Pat. 96,362.

[2] Merling, *Annalen*, 1883, **216**, 348 ; Willstätter, *Berichte*, 1896, **29**, 398 ; 1897, **30**, 2679.

[3] Merling, *Annalen*, 1883, **216**, 343 ; Willstätter, *Berichte*, 1896, **29**, 1579, 1637.

[4] Willstätter, *Berichte*, 1896, **29**, 1581, 1638.

[5] *Ibid.* 1891, **24**, 3108.

bicyclic system composed of a reduced pyridine and a reduced benzene ring having four atoms of carbon in common.

$$CH_2-CH\underline{\quad\quad}CH_2$$
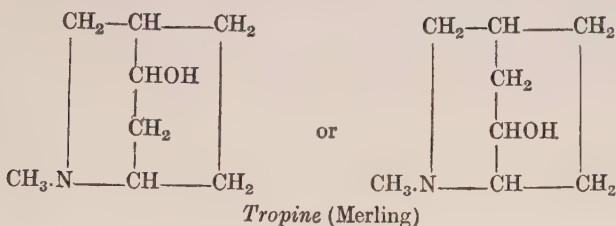
Tropine (Merling)

The first of these formulæ was preferred by Merling on account of its similarity in structure to Fischer's triacetonamine, the phenyl glycollic ester of which exhibits mydriatic action.[1] Merling's formula for tropine satisfactorily explained many of its typical reactions, and it remained in use until Willstätter found that tropinone condensed with benzaldehyde to give a dibenzylidene derivative, with ethyl oxalate to yield diethyltropinone dioxalate, whilst with amyl nitrite it furnished a dioximinotropinone. All these reactions indicated the presence in tropinone of two reactive methylene groups thus : $-CH_2.CO-CH_2-$; and, consequently, that tropine must contain the grouping $-CH_2.CHOH.CH_2-$. On the basis of these observations, Willstätter suggested three possible formulæ for tropine :
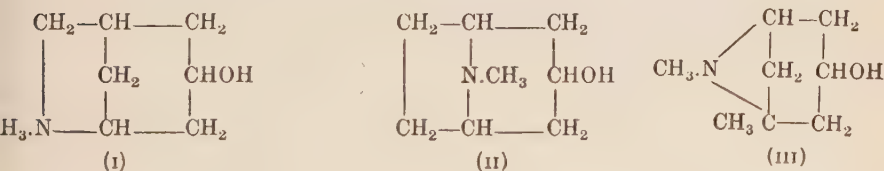
Tropine (Willstätter 1898)

To obtain definite evidence for one of these formulæ, Willstätter[2] applied Hofmann's reaction to tropinic acid, from which he obtained eventually methyltropinate methiodide and from this trimethylamine, methyl alcohol and an unsaturated dibasic seven-carbon acid, which on reduction with sodium amalgam took up four atoms

[1] *Berichte*, 1883, **16**, 1604.
[2] *Ibid.* 1895, **28**, 3271 ; 1898, **31**, 1535, 2498.

of hydrogen, forming pimelic acid. The unsaturated acid, must, therefore, be represented by the following formula :

$$CH:CH.COOH$$
$$CH:CH.CH_2.COOH$$
Piperylenedicarboxylic acid

$$CH_2 \begin{cases} CH_2.CH_2.COOH \\ CH_2.CH_2.COOH \end{cases}$$
Pimelic acid
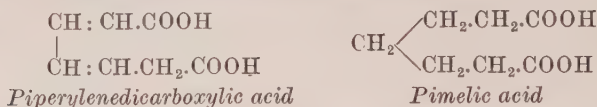
Of the three tropine formulæ given above, the second alone fulfils this condition, and is capable of yielding a seven-carbon open-chain acid of this formula, and this was finally adopted as representing the constitution of tropine. The formulæ of the chief tropine derivatives must, therefore, be written as follows :

$$CH_2—CH——CH$$
$$N.CH_3 \quad CH$$
$$CH_2—CH——CH_2$$
Tropidine

$$CH_2—CH——CH_2$$
$$N.CH_3 \quad CO$$
$$CH_2—CH——CH_2$$
Tropinone

$$CH_2—CH——COOH$$
$$N.CH_3$$
$$CH_2—CH——CH_2.COOH$$
Tropinic acid
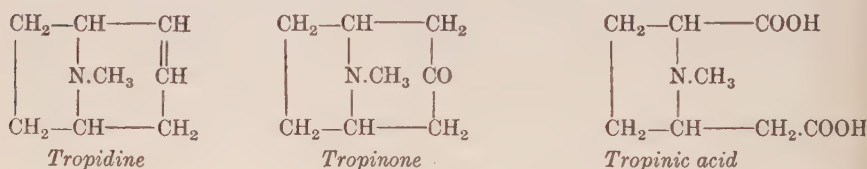
Tropilidene and tropilene (*see* p. 74), produced by (1) exhaustive methylation of tropidinemethiodide, and (2) the action of potassium hydroxide on the methiodide, were regarded by Merling as methylene-dihydrobenzene and tetrahydrobenzaldehyde respectively, but are represented by Willstätter as heptacyclic derivatives of the following formulæ :

$$\begin{array}{c} CH_2 \\ CH \quad CH \\ CH \quad CH \\ CH====CH \end{array}$$
Tropilidene

$$\begin{array}{c} CO \\ CH_2 \quad CH \\ CH_2 \quad CH \\ CH_2——CH_2 \end{array}$$
Tropilene
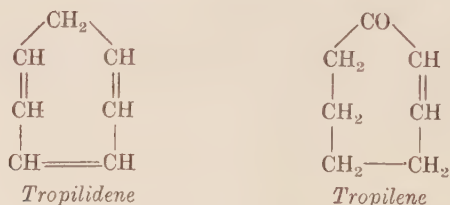
Tropilene readily condenses with one molecule of benzaldehyde and gives an oxymethylene derivative, reactions which establish the existence in its molecule of a —CH_2—CO— group.

Willstätter's view of the constitution of tropine was confirmed by his synthesis of tropidine, tropine, and *pseudo*tropine [1] from the heptacyclic ketone, suberone, as a starting-point.

The suberone was converted into its oxime, and the latter reduced to suberylamine, which was transformed into *cyclo*heptene

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[1] *Berichte*, 1901, **34**, 129, 3163 ; *Annalen*, 1901, **317**, 204, 267, 307 ; 1903, **326**, 1, 23.

by exhaustive methylation. The latter was brominated and the *cyclo*heptene dibromide heated with dimethylamine in benzene, forming dimethylamino-Δ^2-*cyclo*-heptene, which by exhaustive methylation and subsequent distillation, yielded *cyclo*heptadiene identical with dihydrotropilidene, obtainable from dihydrotropidine. The latter hydrocarbon was in turn converted into the dibromide, and this, by heating with quinoline, was transformed into a *cyclo*heptatriene identical with tropilidene (see p. 74), from which, on adding hydrogen bromide in acetic acid, bromo*cyclo*heptadiene was formed. This substance reacts with dimethylamine, forming dimethylamino*cyclo*heptadiene, identical with α-methyltropidine, obtained by Merling by the distillation of tropidinemethylammonium hydroxide.[1]

Suberone

cyclo*Heptene*

cyclo*Heptene dibromide*

hylamino-Δ^2-cycloheptene

cyclo*Heptadiene*
(*Dihydrotropilidene*)

cyclo*Heptadiene dibromide*
(*Dihydrotropilidene dibromide*)

cyclo*Heptatriene*
(*Tropilidene*)

Bromocycloheptadiene
(*Tropilidene hydrobromide*)

α-*Methyltropidine*
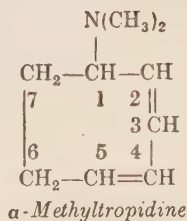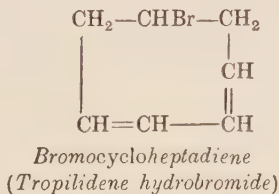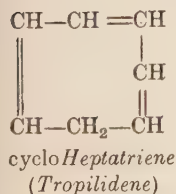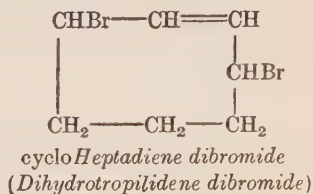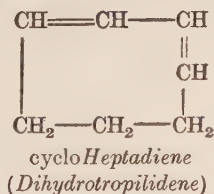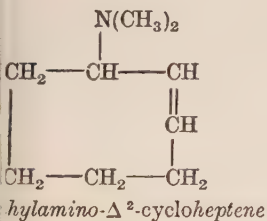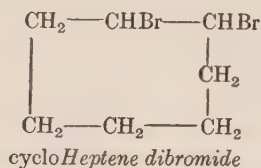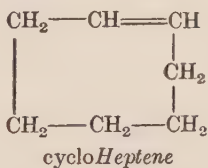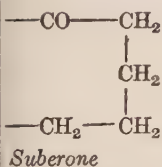
Hofmann[2] had shown that by the action of hydrochloric acid on dimethylpiperidine, methyl chloride and methylpiperidine result; Merling in re-investigating this reaction[3] found that, not methyl-

[1] *Berichte*, 1891, **24**, 3108.
[2] *Ibid.* 1881, **14**, 494, 659.
[3] *Annalen*, 1891, **264**, 310.

piperidine, but the isomeric 2 : 6-dimethylpyrrolidine was formed. The same reaction was applied by Merling when he converted α-methyltropidine into tropidine. It appears, therefore, that as in the reaction of an alkyl haloid with a primary base, a haloid hydrocarbon group in a molecule may enter into reaction with a basic residue in the same molecule, *i.e.*, *intramolecular alkylation* may occur. In the case of a substance represented by the formula given above for α-methyltropidine, if either of the carbon atoms 4 or 5 be chlorinated and the resulting product distilled, intramolecular methylation may be expected to occur with the production of tropidine. This method of reproducing tropidine from α-methyltropidine had already been employed by Merling,[1] but on repeating the experiment Willstätter was unable to obtain a pure tropidine, and so had recourse to the use of Δ^4-dimethylamino*cyclo*heptene, which is formed by the reduction of α-methyltropidine with sodium in alcohol. This was converted into the dibromide by bromine dissolved in hydrobromic acid, and the latter warmed in ethereal solution, when it changed into bromodihydrotropidine methobromide, which, when warmed with alkali, lost a molecule of hydro-

$$N(CH_3)_2$$
$$|$$
$$CH_2-CH-CH_2$$
$$|\qquad\qquad|$$
$$\qquad\qquad CH_2$$
$$|\qquad\qquad|$$
$$CH_2-CH=CH$$

Δ^4-*Dimethylamino*cyclo*heptene* (*α-Methyldihydrotropidine*)

$$CH_2\!\!-\!\!-\!\!CH\!\!-\!\!-\!\!CH_2$$

Br.N⟨CH₃ CH₃

$$CH_2\!\!-\!\!-\!\!CH\!\!-\!\!-\!\!CHBr$$

Bromodihydrotropidine methobromide

$$CH_2\!\!-\!\!-\!\!CH\!\!-\!\!-\!\!CH_2$$

N.CH₃   CH

$$CH_2\!\!-\!\!-\!\!CH\!\!-\!\!-\!\!CH$$
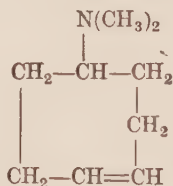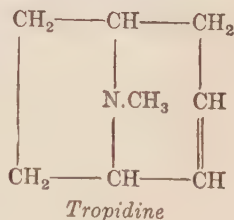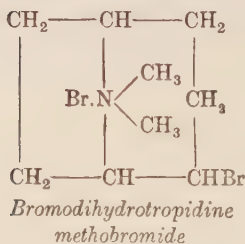
Tropidine

bromic acid, forming tropidinemethobromide. This by the action of potassium iodide passed into the corresponding methiodide, and the latter by digestion with silver chloride gave the methochloride, which on heating furnished tropidine, identical with that obtained from tropine.

[1] *Berichte*, 1891, **24**, 3110.

The conversion of α-methyltropidine into tropidinemethiodide was subsequently achieved by Willstätter in another way.[1] By saturating a solution of the base in hydrochloric acid with hydrogen chloride, the elements of the latter were added on in the $\Delta^{2\cdot3}$ position (formula, p. 79), and the product on treatment with water yielded *pseudo*methyltropine. The latter was next brominated in positions 4 and 5 (formula, p. 79). The dibromide, thus formed, undergoes spontaneous isomerisation into bromo-ψ-tropinemethylammonium bromide, and this on reduction with zinc dust and hydriodic acid yielded, not, as was expected, tropine (or ψ-tropine), but, by elimination of water, tropidine methiodide, from which tropidine and eventually tropine can be obtained as indicated.

$$CH_2—CH(NMe_2)—CH_2 \qquad CH_2—CH———CH_2 \qquad CH_2—CH———CH$$
$$| \qquad\qquad\qquad CHOH \qquad | \quad NMe_2Br \;\; CHOH \qquad | \quad N.Me_2I \qquad CH$$
$$CH_2—CHBr———CHBr \qquad CH_2—CH———CHBr \qquad CH_2—CH———CH_2$$

| pseudo *Methyltropine* dibromide | *Bromo-ψ-tropine methyl-* ammonium bromide | *Tropidine* methiodide |
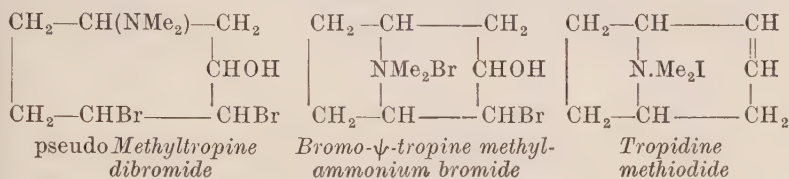
This synthetic tropidine was converted into bromodihydro-tropidine by hydrogen bromide in acetic acid, and the solution heated with 10 per cent. sulphuric acid at 200°–210°, when it passed into *pseudo*tropine[2] identical with the natural base derived from tropacocaine (p. 108), and since the latter may be partially converted into tropine by oxidation to tropinone, and reduction of the latter by zinc dust and hydriodic acid,[3] this complicated series of reactions affords a complete synthesis of tropine and of the tropëines. Combining the formula given above for tropine with that of tropic acid, atropine and hyoscyamine are represented as follows :

$$CH_2———CH———CH_2$$
$$| \qquad *N.CH_3 \quad CH.O.CO—CH \big< {}^{CH_2OH}_{C_6H_5}$$
$$CH_2———CH———CH_2$$

| *Atropine*   and   *Hyoscyamine* |
| (dl-*tropyltropëine*)   (l-*tropyltropëine*) |
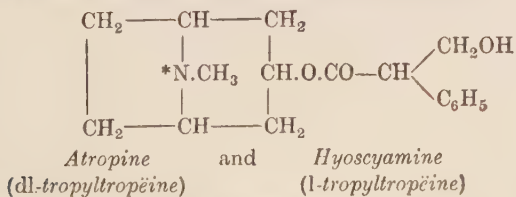
* In norhyoscyamine and noratropine (p. 83) this —CH₃ group is replaced by —H.

The importance of tropinone as a possible starting-point for the

[1] *Annalen*, 1903, **326**, 1.

[2] Willstätter, *Berichte*, 1901, **34**, 3163 ; *Annalen*, 1903, **326**, 23.   *Cf.* Ladenburg, *Berichte*, 1902, **35**, 1159.

[3] Willstätter and Iglauer, *ibid.* 1900, **33**, 1170.

production of the therapeutically valuable alkaloids atropine, hyoscyamine, cocaine, tropacocaine, and the artificial tropëines (p. 73), led Robinson [1] to consider the possibility of preparing this substance by a simpler method than those used by Willstätter and his collaborators. Starting with the idea that the formula for tropinone may be regarded as made up of the formulæ of residues of succindialdehyde, methylamine and acetone, he found that a mixture of these three substances in water, when allowed to stand for thirty minutes produced tropinone which could be detected by means of its characteristic dipiperonylidene derivative (bright yellow needles, m.p. 214°).

| Succindi-aldehyde | Methyl-amine | Acetone | Tropinone |
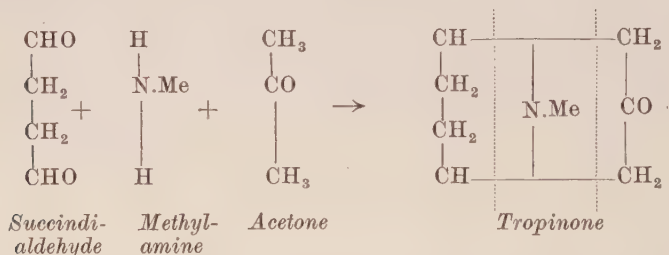
A better yield was obtained when in place of acetone, calcium acetonedicarboxylate was used, the initial product in this case being calcium tropinonedicarboxylate, from which the free dibasic acid is readily isolated and can be decarboxylated by heating in solution, yielding tropinone. This idea has been taken up in Germany, and a number of processes for the production of tropinone derivatives have been described, mostly in patent literature. According to Willstätter and Pfannenstiel,[2] a yield of about 60 per cent. of acetone-dicarboxylic acid can be obtained by treating citric acid with fuming sulphuric acid and the potassium-potassio derivative of the ethyl ester of this acid on electrolysis furnishes ethyl succinyldiacetate (I) which reacts with methylamine acetate to give N-methylpyrrole-
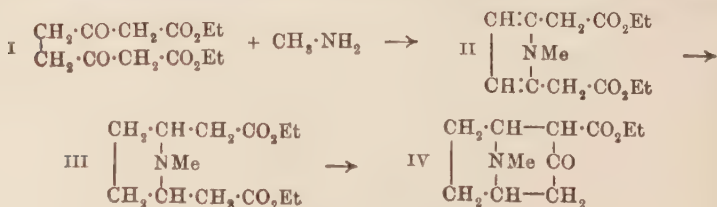
[1] *Trans. Chem. Soc.* 1917, **111**, 762.
[2] *Annalen,* 1921, 422, 1.

$2'_4$: 5-diacetate (II). The latter, probably a mixture of the *cis*- and *cis-trans*-isomerides, is then reduced to the corresponding pyrrolidine ester (III) which, when heated in cymene solution with sodium is condensed to ethyl tropinonecarboxylate (IV), and the latter, on boiling with 10 per cent. sulphuric acid, yields tropinone [1] from which tropine (p. 75) and ecgonine (p. 107) can be obtained.

Norhyoscyamine, $C_{16}H_{21}O_3N$. Carr and Reynolds [2] have shown that this alkaloid occurs in minute quantity in *Scopolia japonica*, *Datura metel*, *D. meteloides*, *Duboisia myoporoides*, and *Mandragora vernalis*, and Petrie has found it in *Solandra longiflora*.[3]

The alkaloid is best separated from the accompanying hyoscyamine first by extracting most of the former with ether (*see* general method, p. 62), and then by crystallising the mixed oxalates from water, that of norhyoscyamine separating first. The alkaloid crystallises from acetone in colourless prisms, m.p. 140°, $[\alpha]_D - 23 \cdot 0°$ in 50 per cent. alcohol, is soluble in alcohol or chloroform, less so in ether or acetone, and sparingly in water (1 in 270 at 14° C.). It is a strongly alkaline base and can readily be titrated. The hydrochloride, B.HCl, forms rosettes of needles, m.p. 207°; the sulphate, $B_2.H_2SO_4.3H_2O$, silky needles, m.p. 249°; and the oxalate, $B_2.H_2C_2O_4$, long prisms, m.p. 245°–246°, soluble in water (1 in 20 at 15°). The aurichloride, B.HAuCl$_4$, separates from dilute alcohol in golden yellow scales, m.p. 178°–179°, and the platinichloride, $B_2.H_2PtCl_6.3H_2O$, forms handsome, reddish-yellow prisms of indefinite melting-point. The picrate crystallises in needles, m.p. 220°.

Norhyoscyamine yields a nitrosoamine, and is converted by methyl iodide into hyoscyamine. Further, in presence of alkali, it undergoes racemisation to noratropine (*see* p. 84), and on hydrolysis by baryta water, yields tropic acid and nortropine (tropigenine), $C_7H_{13}ON$ (m.p. 161°, b.p. 233°).

Norhyoscyamine closely resembles the pseudohyoscyamine isolated from *Duboisia myoporoides* by E. Merck,[4] and later from

[1] Willstätter and Bommer, *Annalen*, 1921, **422**, 15. *Cf. German Patent*, 302,401 (*Chem Soc. Abstr.* 1921 [i], 680). For variants and developments, *see British Patents* 153,917, 164,757 and 177,807 (*Chem. Soc. Abstr.* 1922 [i], 567, 568); *United States Patents* 1,419,091, 1,419,092 (*Chem. Soc. Abstr.* 1922 [i], 938); *German Patents* 354,696, 354,950 and 389,359 (*Chem. Soc. Abstr.* 1922 [i], 1173).

[2] *Trans. Chem. Soc.* 1912, **101**, 946.

[3] *Proc. Linn. Soc. N.S.W.* 1907, **32**, 1789; 1917, **41**, 815.

[4] *Arch. Pharm.* 1893, **231**, 117.

Mandragora officinarum by Hesse,[1] and Carr and Reynolds suggest that they are identical, which seems likely in view of the properties ascribed to pseudohyoscyamine (needles, m.p. $133°$–$134°$, $[\alpha]_D - 21°$), and its picrate, m.p. $220°$.

NORATROPINE, $C_{16}H_{21}O_3N$.   When a solution of norhyoscyamine (5·2 grm.) in 52 c.c. of alcohol containing 0·416 grm. of sodium hydroxide is allowed to stand for sixteen hours, about 20 per cent. of it is hydrolysed, but the rest is racemised to noratropine, which can be isolated in the ordinary way, and on recrystallisation from dry acetone, melts at $113°$–$114°$ C. ; it is readily soluble in alcohol, chloroform or ethyl acetate, less so in ether, acetone or water, is optically inactive and forms a monohydrate, m.p. $73°$.   The hydrochloride, $B.HCl$, separates from dry alcohol on addition of acetone in silky filaments, m.p. $193°$; the sulphate, $B_2.H_2SO_4$, in long needles, m.p. $257°$, from water (solubility 1 in 9·5 c.c.); the oxalate, $B_2.H_2C_2O_4$, m.p. $247°$–$248°$, crystallises best from hot water (solubility 1 in 130 c.c. at $15°$); the aurichloride forms dull rosettes of opaque yellow needles, m.p. $157°$, from dilute alcohol, and resembles atropine aurichloride in melting under water. The picrate crystallises in needles, m.p. $227°$.   On treatment with methyl iodide noratropine is converted into atropine.

The relationship of norhyoscyamine and noratropine to hyoscyamine may be represented as follows :

$$
\begin{array}{ll}
\mathrm{CH_2 \cdot CH \cdot CH_2} \qquad \mathrm{C_6H_5} & \qquad \mathrm{CH_2 \cdot CH — CH_2} \qquad \mathrm{C_6H_5} \\
\qquad \mathrm{NH \; CH \cdot O \cdot CO \cdot CH} & \qquad\; \mathrm{NMe \; CH \cdot O \cdot CO \cdot CH} \\
\mathrm{CH_2 \cdot CH \cdot CH_2} \qquad \mathrm{CH_2 \cdot OH} & \qquad \mathrm{CH_2 \cdot CH — CH_2} \qquad \mathrm{CH_2 \cdot OH}
\end{array}
$$

Norhyoscyamine or *Noratropine*   *Hyoscyamine* or *Atropine*
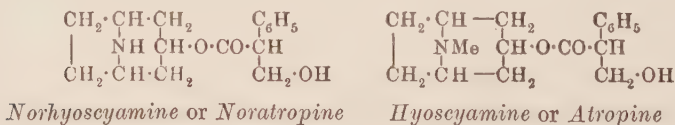
Mandragorine.   An alkaloid to which this name was assigned was isolated by Ahrens [2] from the root of *Mandragora officinarum*, a plant whose sedative properties were well known to the ancients, and which, in the form of " wine of mandragora," was probably the first anæsthetic used in surgical operations.[3]   Thoms and Wentzel [4] have shown, however, that Ahren's mandragorine is a mixture of hyoscyamine and hyoscine, with perhaps a minute quantity of a third alkaloid.   Hesse has, however, asserted that this root contains,

[1] *J. pr. Chem.* 1901 [iii], **64**, 274.
[2] *Berichte*, 1889, **22**, 2159.
[3] *Asclepiad*, June, 1888.
[4] *Berichte*, 1901, **34**, 1023.

in addition to hyoscyamine and hyoscine, pseudohyoscyamine (probably norhyoscyamine, *see* p. 83), and a new mandragorine, $C_{15}H_{19}O_2N$, which furnishes a crystalline aurichloride, m.p. 124°–126°; on hydrolysis, tropic acid and a base resembling tropine are formed.[1]

Meteloidine, $C_{13}H_{21}O_4N$, was found by Pyman and Reynolds with atropine and hyoscine, in *Datura meteloides*.[2] It crystallises from benzene in tabular needles, m.p. 141°–142°, $[\alpha]_D$ 0°, is readily soluble in alcohol or chloroform, sparingly so in water, ether, or benzene. The hydrobromide, $B.HBr.2H_2O$, forms chisel-shaped needles, m.p. 250° (*dry*); the aurichloride, $B.HAuCl_4 . \frac{1}{2}H_2O$, m.p. 149°–150°, forms short yellow needles from dilute alcohol; the picrate has m.p. 177°–180°, and forms hexagonal plates. Meteloidine is physiologically inactive.

On hydrolysis by baryta the alkaloid is resolved into tiglic acid, $CH_3.CH : C(CH_3).COOH$, and a new base, Teloidine, $C_8H_{15}O_3N$, which crystallises from boiling acetone diluted with a little water in chisel-shaped needles containing $1H_2O$, m.p. 168°–169° (*dry*). It is not volatile; the hydrochloride, m.p. above 300°, hydrobromide, m.p. 295°, and aurichloride, $B.HAuCl_4.\frac{1}{2}H_2O$, m.p. 225°, are all crystalline. King[3] has made the interesting suggestion that tropine, $C_8H_{15}ON$, oscine, $C_8H_{13}O_2N$, and teloidine, $C_8H_{15}O_3N$, are related to each other in the following way :
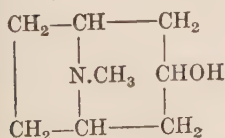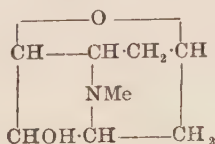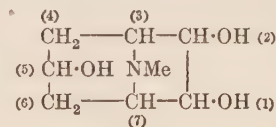
Tropine   *Oscine*   *Teloidine* (King)

Hyoscine (*Scopolamine, Atroscine*), $C_{17}H_{21}O_4N$. The name hyoscine has been applied to two distinct substances. It was first suggested by Höhn and Reichardt[4] for the basic hydrolytic product of hyoscyamine, now known as tropine. It was subsequently used by Ladenburg[5] for an alkaloid, stated to be isomeric with atropine, $C_{17}H_{23}O_3N$, isolated from the mother liquors of hyoscyamine. This

[1] *J. pr. Chem.* 1901 [iii], **64**, 274.
[2] *Trans. Chem. Soc.* 1908, **93**, 2077.
[3] *Ibid.* 1919, **115**, 487.
[4] *Annalen*, 1871, **157**, 98.
[5] *Ibid.* 1880, **206**, 209.

was found by Schmidt,[1] Hesse,[2] and others, to be identical with scopolamine, $C_{17}H_{21}O_4N$, obtained by Schmidt from *Scopolia japonica*.[3] Although the name hyoscine has priority and has passed into commercial use for this alkaloid, Schmidt's name scopolamine is also employed, especially in Germany, and there is a tendency in some quarters to use scopolamine for *dl*-hyoscine which Hesse obtained and called atroscine (*see below*).

The occurrence of hyoscine in solanaceous plants is shown in the table on p. 63.

The alkaloid is usually obtained from the mother liquors left in the preparation of hyoscyamine, but *Datura metel*, which contains hyoscine as its chief constituent, is a particularly satisfactory material from which to prepare this alkaloid. In using the general method of extraction (p. 62), it is advisable to liberate hyoscine with sodium bicarbonate, and to neutralise the crude alkaloid with hydrobromic acid. On concentrating the solution hyoscine hydrobromide crystallises out.

The free base is a syrup, soluble in ordinary solvents, least readily in light petroleum or benzene. It is lævorotatory, $[\alpha]_D^{20} - 18°$ in alcohol, $- 28°$ in water. The salts crystallise well : the hydrobromide, $B.HBr.3H_2O$, m.p. 193°–194° (*dry*), $[\alpha]_D - 15.72°$ in alcohol, $- 25.93°$ (anhydrous salt) in water,[4] crystallises in rhombic tablets, is readily soluble in water (1 in 1.5 at 25°) or alcohol (1 in 16 at 25°), sparingly in chloroform (1 in 750 at 25°), insoluble in ether. It is bitter and acrid to the taste, and is slightly acid to litmus. This salt is that mostly used in medicine. The aurichloride, $B.HAuCl_4$, m.p. 208°–209° (*decomp.*) crystallises in needle-shaped growths serrated on both edges, and is sparingly soluble in water containing hydrochloric acid (1 in 510 at 50° for a solution containing 10 c.c. of hydrochloric acid, sp. gr. 1.19 in 1,000 c.c. of water). The auribromide, $B.HAuBr_4$, m.p. 191°–192°, forms long, rectangular chocolate-red leaflets from boiling 2.5 per cent. hydrochloric acid. The picrate crystallises in slender, primrose-yellow needles, m.p. 187°–188°, but on recrystallisation from boiling water, forms flat irregular six-sided scales, m.p. 187.5°–188.5° (191°–192° *corr.*).

Hyoscine, like hyoscyamine, is readily racemised by the action

[1] *Arch. Pharm.* 1892, **230**, 207 ; 1894, **232**, 409.
[2] *Annalen.* 1892, **271**, 120 ; 1893, **276**, 84.
[3] *Arch. Pharm.* 1890, **228**, 139, 435. *Cf.* Dunstan and Chaston, *Pharm. Journ.* 1889 [iii], **20**, 461.
[4] King, *Trans. Chem. Soc.* 1919, **115**, 504. *Cf.* Carr and Reynolds, *ibid.* 1910, **97**, 1330.

PLATE II.
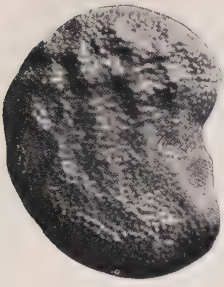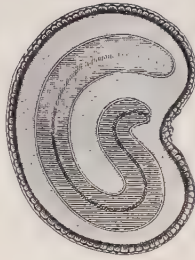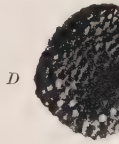
FIG. 1.—Stramonium seed. Magnified. (*B*, after Moeller.)

FIG. 2.—Henbane seed. *A*, e... fruit. *B*, the same cut verti... *C*, seed, cut longitudinally. (... ssen.) *D*, seed, showing retic... surface. Magnified.

FIG. 3.—Belladonna root. *a*, portion of young root, natural size; *b*, transverse section of the same, magnified; *c*, transverse section of the upper part of the root, magnified. (Holmes.)

of dilute alkalis, and for this reason commercial hyoscine hydro-bromide not infrequently contains inactive salt. Hesse [1] isolated from such material an optically inactive alkaloid, isomeric with hyoscine, which he named ATROSCINE. According to Schmidt [2] this substance was dl-hyoscine, and Gadamer [3] showed that Hesse's atroscine and Schmidt's dl-hyoscine were respectively di- and mono-hydrates of the same alkaloid. [4]

dl-Hyoscine may be prepared by the action of dilute sodium hydroxide solution in alcohol, on the $lœvo$-form at atmospheric temperature. L. Merck has stated that hyoscine hydrobromide from henbane seed has a rotation of $-24°$ to $-25°$, whilst that from *Scopolia* rhizome has a rotation of $-13·47°$, so that the latter appears always to contain some racemic base. [5] From such material, according to Gadamer, [6] the inactive alkaloid can be separated by adding sodium carbonate to the aqueous solution, and extracting with a mixture of chloroform and ether. On rubbing the residue with alcohol and water and cooling, the dihydrate (Hesse's atroscine), rosettes of needles, m.p. $37°–38°$ ($36°–37°$ Hesse; prisms, $38°–40°$ King), forms, whilst seeding with the monohydrate (Schmidt's dl-hyoscine) leads to the separation of the latter form in mono-clinic needles, m.p. $56°–57°$. King [7] prepared from works residues, accumulated in the manufacture of l-hyoscine, the dextro-form of the alkaloid, and by combining this with an equal weight of the lævo-isomeride, obtained the dl-form, and was thus enabled to characterise the three forms of the alkaloid and some of their chief derivatives. The results of this careful comparison are shown in the table on p. 88.

The reactions of hyoscine are for the most part similar to those of atropine and hyoscyamine, but it gives a white precipitate with mercuric chloride. It may best be distinguished from these alkaloids by means of its aurichloride or picrate.

When warmed with barium hydroxide, dilute alkalis or acids, hyoscine is hydrolysed, yielding tropic acid and a new base, $C_8H_{13}O_2N$, oscine or scopoline. Depending on the conditions of

[1] *Berichte*, 1896, **29,** 1776.

[2] *Arch. Pharm.* 1898, **236,** 9, 47.

[3] *Ibid.* 1898, **236,** 382.

[4] *Cf.* Hesse, *Annalen*, 1899, **309,** 75; *Journ. prakt. Chem.* 1901 [ii], **64,** 353; 1902 [ii], **66,** 194.

[5] *Cf.* Schmidt, *Arch. Pharm.* 1898, **236,** 54.

[6] *Arch. Pharm.* 1898, **236,** 382. *Cf.* Hesse, *Journ. prakt. Chem.* 1901 [ii], **64,** 353; 1902 [ii], **66,** 194; and Kunz-Krause, *ibid.*, 1901 [ii], **64,** 569.

[7] *Trans. Chem. Soc.* 1919, **115,** 476.

Derivative.		l-Hyoscine.	d-Hyoscine.	dl-Hyoscine.
Base . . .	Character	Syrup.	Syrup.	Prisms containing $2H_2O$, m.p. $38°$–$40°$ (corr.). Anhydrous substance, syrup.[1]
Hydrobromide	Character	Rhombic tablets with $3H_2O$	Rhombic tablets with $3H_2O$	Rhombic tablets with $3H_2O$, efflorescent.
	M.p. (dry salt). .	$193°$–$194°$ $197°$–$198°$ (corr.).	$193°$–$194°$ $197°$–$198°$ (corr.).	$181°$–$182°$ $185°$–$186°$ (corr.).
	$[a]_D$ (dry salt in water).	$- 25·9°$	$+ 26·3°$	—
Picrate	Character	Slender matted needles.	Slender matted needles.	Needles.
	M.p.. .	$187°$–$188°$ $191°$–$192°$ (corr.).[2]	$187°$–$188°$ —	$173·5°$–$174·5°$ $177·5°$–$178·5°$ (corr.).[2]
Aurichloride .	Character	Needles, both edges serrated.	Needles, both edges serrated.	Needles, one edge serrated.
	M.p.. .	$204°$–$205°$ $208°$–$209°$ (corr.).[3]	$204°$–$205°$ $208°$–$209°$ (corr.).[3]	$214°$–$215°$ $218°$–$219°$ (corr.).[3]
Auribromide .	Character	Chocolate-red leaflets.	—	Chocolate-red leaflets.
	M.p.. .	$187°$–$188°$ $191°$–$192°$ (corr.).[4]	— —	$209°$–$210°$ $213°$–$214°$ (corr.).[4]

experiment, the tropic acid obtained may be either the pure l-form or the partially racemised acid, but the oscine obtained is invariably inactive. It appeared to follow from this that the three forms of hyoscine known are respectively l-tropyl-dl-oscine, d-tropyl-dl-oscine and dl-tropyl-dl-oscine, the optical activity of the first two being conditioned solely by the activity of the tropyl radicle. This subject has been thoroughly discussed by King,[5] who has confirmed

[1] *Cf.* Hesse, *Berichte*, 1896, **29**, 1776 ; Gadamer, *Arch. Pharm.* 1898, **236**, 382.
[2] *Cf.* Carr and Reynolds, *Trans. Chem. Soc.* 1912, **101**, 949 ; Schmidt, *Arch. Pharm.* 1894, **232**, 409 ; Finnemore and Braithwaite, *Pharm. Journ.* 1912, **89**, 136.
[3] *Cf.* Schmidt, *Arch. Pharm.* 1910, **248**, 641 ; Hesse, *Journ. prakt. Chem.* 1901 [ii], **64**, 274 ; Thoms and Wentzel, *Berichte*, 1901, **34**, 1023 ; Finnemore and Braithwaite, *Pharm. Journ.* 1912, **89**, 136,
[4] *Cf.* Jowett, *Trans. Chem. Soc.* 1897, **71**, 680,
[5] *Trans, Chem. Soc.* 1919, **115**, 483,

his own results, arrived at from deracemisation of *dl*-hyoscine by means of *d*-α-bromo-π-camphorsulphonic acid by converting *l*-hyoscine (I) into β-chlorohydratropyloscine (II), and then into apohyoscine [1] (III) (thus destroying the asymmetry of the tropyl radicle).

$$\begin{array}{ccc}
\begin{array}{c} CH_2 \cdot OH \\ Ph \cdot CH \cdot CO_2 \cdot C_8H_{12}ON \end{array} & \rightarrow & \begin{array}{c} CH_2Cl \\ Ph \cdot CH \cdot CO_2 \cdot C_8H_{12}ON \end{array} & \rightarrow & \begin{array}{c} CH_2 \\ Ph \cdot C \cdot CO_2 \cdot C_8H_{12}ON, HCl. \end{array} \\
(I) & & (II) & & (III)
\end{array}$$
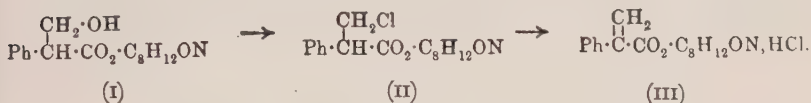
and showing that the resulting apohyoscine was not only inactive, but could not be resolved into optically active forms. The same author has, however, shown that oscine itself can be resolved into *d*- and *l*-forms, and some years previously benzoyloscine had been deracemised by Tutin.[2] Benzoyl-*d*-oscine and its *l*-isomeride, furnish *d*- and *l*-oscine respectively, and not the inactive base when hydrolysed either by sodium hydroxide or hydrochloric acid. These anomalies are explained later (p. 92).

Oscine (Scopoline), $C_8H_{13}O_2N$. This substance, probably first obtained by Ladenburg by the hydrolysis of hyoscine, was first examined by Hesse,[3] who assigned to it the foregoing formula, and later by Luboldt.[4] It forms colourless, hygroscopic prismatic crystals, m.p. 109°, from ether or light petroleum, and boils at 241°–243°. As already stated the racemic form of oscine is always obtained by hydrolysis of hyoscine, but this has been resolved into the *d*- and *l*-forms by King [5] by crystallisation of the *d*-hydrogen tartrates. The characters of the three forms of oscine and of their picrates and hydrochlorides, are summarised in the table on p. 90.

Though much work had been done towards elucidating the constitution of oscine, it was not until 1915 that rapid progress began to be made towards reaching a formula, which would account satisfactorily for its reactions. Up to that time it had been established that oscine was a tertiary base, containing one hydroxyl group, and that the second oxygen atom was probably present in an etheric linkage. It was also known that on oxidation with chromic

[1] *Trans. Chem. Soc.* 1919, **115**, 974. *Cf.* Willstätter and Hug, *Zeit. physiol. Chem.* 1912, **79**, 146.
[2] *Trans. Chem. Soc.* 1910, **97**, 1793.
[3] *Annalen*, 1892, **271**, 114 ; 1893, **276**, 84,
[4] *Arch. Pharm.* 1898, **236**, 11.
[5] *Trans. Chem. Soc.* 1919, **115**, 491,

Derivative.	Characteristics.	*l*-Oscine.	*d*-Oscine.	*dl*-Oscine.
Base . . .	Character .	Needles.	Needles.	Needles or tablets.
	M.p.. . .	109·5°	109·5°	109°–110°
	$[a]_D$ in water	— 52·4°	+ 54·8°	—
Picrate . .	Character .	Dimorphous : rhombs and needles.	Dimorphous : rhombs and needles.	Flattened rhombs
	M.p.. . .	237°–238°	237°–238°	237°–238°
Hydrochloride	Character .	Prisms in warty masses. Deliquescent.	Prisms in warty masses. Deliquescent.	Prisms in warty masses (anhydrous). Tablets (hydrated).
	M.p.. . .	273°–274° 281°–282° (*corr.*).	273°–274°	273°–274°
	$[a]_D$ (basic ion) in water.	— 24·2°	+ 24·0°	—

acid, oscine furnished scopoligenine,[1] $C_7H_{10}O_2$: NH, analogous with the tropigenine yielded by tropine (p. 76) ; but what eventually proved to be the most fruitful line of work was Schmidt's observation [2] that on heating at 130° with excess of saturated hydrobromic acid, it formed hydrobromoscopoline hydrobromide, $C_8H_{14}O_2NBr$. HBr (plates, m.p. 202°), which on reduction yielded dihydroscopoline, $C_8H_{15}O_2N$ (aurichloride, m.p. 200°–201°).[3] The latter was shown to contain two hydroxyl groups, and on oxidation with chromic acid gave a dibasic acid [4] (scopolic acid, Hess), which was eventually identified as *N*-methylpiperidine-2 : 6-dicarboxylic acid [5] by means of its methyl ester methiodide, first prepared by Willstätter and Lessing,[6] thus indicating that dihydroscopoline is a dihydroxytropane, which brings it into close relationship with tropine.

In the meantime, Hess and his collaborators [7] had independently obtained and synthesised the same acid and drawn the same conclusion regarding dihydroscopoline, which Hess confirmed by

[1] As most of the work on the constitution of oscine has been done in Germany, where the synonym scopoline is in use, the names of the products isolated in the course of this work are derived from scopoline.

[2] *Apoth. Zeit.* 1902, **17**, 592 (*Chem. Soc. Abstr.* 1903 [i], 51).

[3] *Loc. cit.* and *Arch. Pharm.* 1905, **243**, 559 ; *Cf.* Hess and Suchier, *Berichte*, 1915, **48**, 2057.

[4] *Ibid.* 1909, **247**, 79.

[5] *Ibid.* 1916, **253**, 497. *Cf.* Hess and Wissing, *Berichte*, 1915, **48**,1907.

[6] *Berichte*, 1902, **35**, 2065.

[7] *Ibid.* 1915, **48**, 1907, 2057.

showing that it yields tropane on reduction with hydriodic acid and phosphonium iodide at 200°.[1]

$$CH_2——CH——CHOH \quad\quad CH_2——CH——CH_2 \quad\quad CH_2—CH——CH_2$$
$$CH_2 \quad NMe \quad\quad\quad CH_2 \quad NMe \quad\quad HO.CH \quad NMe$$
$$CH_2——CH——CHOH \quad\quad CH_2——CH——CH_2 \quad\quad CH_2—CH——CH_2$$
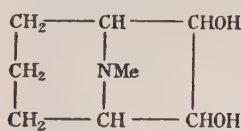
Dihydroscopoline	*Tropane*	*Tropine*
(Schmidt)		
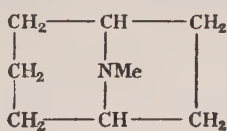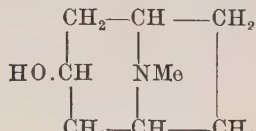
It was now clear that in oscine (scopoline) one oxygen atom was attached to carbon atom 1[2] or 2 in the tropane nucleus as a hydroxyl group, and the other to carbon atom 5 or 6 as an oxide, but the other position of attachment of the second oxygen valency remained to be cleared up, and Hess investigated the fission of scopoline by Hofmann's method for this purpose.[3] Unfortunately the reaction does not proceed smoothly, and the products show that the amino group is not the only one affected, the oxygen bridge being ruptured and reconstituted, substances containing two ethylenic linkages are formed, and an *O*-methyl ether is one of the end products. In an attempt to account for these anomalous results, Hess suggested that the oxygen bridge must lie between positions 2 and 7 (*see below*), which accounts for its rupture in the first stage of the Hofmann reaction. Gadamer and Hammer,[4] repeating this work under somewhat different conditions, came to the conclusion that the results could be better explained by assuming that the oxygen bridge lies between positions 2 and 5, a suggestion already made by King,[5] and subsequently accepted by Hess and Wahl.[6]

$$CH——CH—CH_2 \quad\quad\quad CH——CH·CH_2·CH$$
$$O \quad NMe \quad CH_2 \quad\quad\quad NMe$$
$$CHOH—C——CH_2 \quad\quad\quad CHOH·CH——CH_2$$
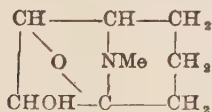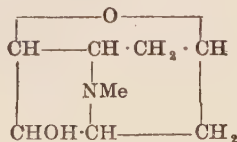
Hess (1919)	King (1919); Gadamer (1921)

With King's formula a more rational explanation of the results of the application of the Hofmann reaction to oscine becomes

[1] *Berichte*, 1918, **51,** 1007.
[2] For system of numbering, *see* teloidine formula, p. 85.
[3] *Berichte.* 1919, **52B,** 1947.
[4] *Arch. Pharm.* 1921, **259,** 110.
[5] *Trans. Chem. Soc.* 1919, **115,** 486.
[6] *Berichte,* 1922, **55B,** 1972. *Cf.* Gadamer, *loc. cit.* and *Berichte,* 1923, **56,** 130.

possible.[1] The products obtained by careful distillation of the ammonium base under reduced pressure consist of four isomeric bases, $C_9H_{15}O_2N$. One of these is demethylscopolinone. The other three (α-, β-, and γ-demethylscopolines) have been isolated either as such or as the picrates of the dihydro-products. The α- and β-dihydro-products on conversion by thionyl chloride into the corresponding chlorides, and treatment of these with sodium methoxide, furnish methyl ethers, which on further degradation yield trimethylamine and non-nitrogenous substances. The α-, β-, and γ-dihydro-products are all reduced by phosphorus and hydriodic acid to the same amine, which contains two atoms of hydrogen less than the expected dimethylsuberylamine.

These results leave unexplained King's observation that whilst oscine and benzoyloscine can each be resolved into two optically active forms, dl-hyoscine is only able to be resolved into two forms, the optical activities of which are conditioned solely by the tropyl radicle in each, and are in no way due to the basic residue in the alkaloid (see p. 88). King[2] considered that this might be due to the basic residue in hyoscine having a symmetrical and, therefore, different configuration from that of oscine and capable of yielding the latter on hydrolysis, but preferred to regard the d- and l-hyoscines as partial racemates. Hess and Wahl,[3] however, succeeded in showing that the first of these two views was probably correct. They were unable to synthesise either l-hyoscine (from l-tropic acid and dl-oscine) or apohyoscine (from atropic acid and oscine), but were able to prepare by reduction of apohyoscine a deoxyhyoscine and to show that this existed in only one racemic form, although on hydrolysis it furnished dl-oscine and deoxytropic acid (phenylpropionic acid). On the other hand, they found that esterification of dl-oscine with dl-deoxytropic acid (α-phenylpropionic acid) produced two racemic alkaloids (deoxytropylscopoleines) neither of which was identical with deoxyscopolamine. To explain these facts, they adopted the suggestion already considered by King that in hyoscine the amino-alcohol is symmetrical, and is converted into oscine in the process of hydrolysis. This idea was shown to be well founded by Willstätter and Berner,[4] who found that hyoscine is slowly hydrolysed by pancreatic lipase, in presence of ammonium

[1] Berichte, 1922, 55B, 1972. Cf. Gadamer, loc. cit. and Berichte, 1923, 56, 139.

[2] Loc. cit. Cf. Gadamer and Hammer, Arch. Pharm. 1921, 259, 110.

[3] Berichte, 1922, 55B, 1972.

[4] Ibid. 1923, 56B, 1079.

chloride as a buffer, to SCOPINE, $C_8H_{13}O_2N$ (with partial conversion of the latter into the isomeric asymmetrical oscine) which is the real basic hydrolytic product of hyoscine. Scopine crystallises in long needles, m.p. 76°, is optically inactive, and is readily converted, when heated, or under the influence of acids or especially of alkalis, into oscine. The hydrochloride crystallises in leaflets, and the picrate in thin leaflets, m.p. 231°. Scopine is clearly distinguished from oscine by the characters of its platinichloride and aurichloride.

		Platinichloride.	*Aurichloride,*
Scopine	.	$B_2.H_2PtCl_6.2H_2O$ long, domatic prisms, m.p. 219°.	$B.HAuCl_4.\frac{1}{6}H_2O$ small prisms, m.p. 216° (*decomp.*).
Oscine	.	$B_2.H_2PtCl_6.1H_2O$ plates, m.p. 203°.	$B.HAuCl_4.\frac{1}{2}H_2O$, prismatic plates, m.p. 220° (*decomp.*)

The formulæ of hyoscine and its real (scopine) and apparent (oscine) basic hydrolytic products may, therefore, now be written thus :

Hyoscide   *Scopine*   *Oscine*
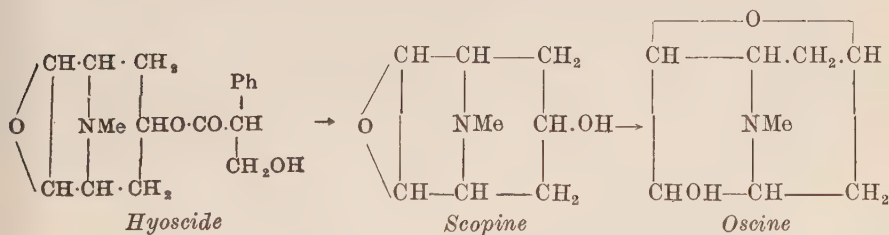
Tetramethyldiaminobutane, $N(CH_3)_2.CH_2.CH_2.CH_2.CH_2.N(CH_3)_2$. This diamine was isolated in 1907 by E. Merck from the secondary bases of *Hyoscyamus muticus*, and was investigated by Willstätter and Heubner.[1] It is a colourless liquid, $D^{15°}$ 0·7941, b.p. 169°, miscible in all proportions with water, strongly alkaline in reaction, optically inactive, and possesses a pungent acrid taste. The hydrochloride, $C_8H_{20}N_2.2HCl$, forms triangular prisms, m.p. 273° (*decomp.*) the platinichloride, $B.H_2PtCl_6.2H_2O$, prisms, m.p. 234° (*decomp.*), and the aurichloride, golden-yellow prisms, m.p. 206°–207° (*decomp.*) from hot water. The substance is not poisonous to frogs or rabbits in moderate doses. It absorbs two molecules of methyl iodide, forming hexamethyltetramethylenediammonium iodide, $MeI.NMe_2.CH_2.CH_2.CH_2.CH_2.NMe_2.MeI$, which on distillation with silver

[1] *Berichte,* 1907, **40**, 3869.

oxide yields butadiene and trimethylamine. Hexamethyltetra-
methylenediammonium chloride, identical in all respects with that
obtainable from the iodide mentioned above, was prepared by
methylating putrescine (1 : 4-diaminobutane), and this on distilla-
tion furnished N-methylpyrrolidine methochloride. These reactions
show that the base from *H. muticus* must be tetramethyldiamino-
butane ; its occurrence is of interest from the fact that by distilla-
tion of its dimethochloride, it can so readily be converted into a
pyrrolidine derivative, and that hyoscyamine, the chief alkaloid
of *H. muticus*, contains a pyrrolidine ring in its nucleus.

ALKALOIDS OF *ERYTHROXYLON COCA*.

The genus *Erythroxylon*, which yields this series of alkaloids,
comprises about eighty species, of which only four or five have been
completely examined. The habitat of these plants is principally
the western side of South America, and although indigenous species
occur in India, Africa and Australia, they have at present no economic
value, and the attention of coca cultivators is chiefly devoted to
three kinds derived originally from Bolivia and Peru, viz. : [1]

Erythroxylon Coca, Lam. (Bolivian or Huanuco coca).

Erythroxylon Coca, var. *Novo-granatence* (*E. Carthagense*, Jacq).

Erythroxylon Truxillense, Rusby (Peruvian or Truxillo leaves).

Four kinds of coca leaves are known in the London market :
(1) Huanuco (Bolivian), (2) Truxillo (Peruvian), (3) Java, (4) Ceylon.
According to Rusby, (1) is from *E. Coca*, Lam., (2) and (3) are from
E. Truxillense, Rusby, and (4) is from *E. Carthagense*, Jacq. This
classification is placed in some doubt by the fact that the Peruvian
leaves contain a large proportion of cocaine, whilst the Java leaves
are stated to contain little or none. [2] It is improbable, therefore,
that these two varieties are derived from the same species. Further,
consignments of Ceylon leaves are often described as either of
" Truxillo character " or " Huanuco character," and samples
examined by Professor Greenish were indistinguishable from Truxillo
leaves, and on examination proved to contain a large proportion of
cocaine. It seems likely, therefore, that Ceylon leaves are of the
same botanical origin as Peruvian leaves, [3] whilst those of Java are
from a distinct species, or at least from a well-marked variety of
E. Truxillense.

[1] Rusby, *Druggists' Circular and Chemists' Gazette*, Nov. 1900, p. 220.
Cf. Holmes. *Pharm. Journ.* Jan. 5, 1901, p. 4, and Jan. 26, 1901, p. 81.
[2] *Cf.* however, de Jong, *Chem. Weekbl.* 1908, **5**, 666.
[3] *Bull. Imp. Inst.* 1912, **10**, 37.

In South America coca leaves are chewed with lime by the Indians as a stimulant, and are largely exported to Europe for use in medicine and for the preparation of cocaine. Crude cocaine is also manufactured in Peru and exported to be refined. Coca leaves come principally from Java.

The alkaloids obtained from coca leaves fall naturally into four groups, as follows :

(1) The *cocaines*, which on hydrolysis yield ecgonine, benzoic, cinnamic, or truxillic acid, and methyl alcohol.

> Cocaine : *Methylbenzoylecgonine.*
> Cinnamylcocaine : *Methylcinnamoylecgonine.*
> α-Truxilline : *Methyl-α-truxilloylecgonine.*
> β-Truxilline : *Methyl-β-truxilloylecgonine.*

(2) The pseudo*tropëines* are closely related to the tropëines (p. 73), and are easily hydrolysed into an acid and the basic alcohol *pseudo*tropine, a stereoisomeride of tropine. They are represented by

> Tropacocaine : *Benzoyl*pseudo*tropëine.*

(3) The *acylecgonines* are acyl esters of ecgonine, and by hydrolysis furnish this base and an acid, and are represented by

> *Benzoylecgonine.*

(4) The *hygrines* are volatile alkaloids of simpler structure than the foregoing and include :

Hygrine (low boiling). *Cuscohygrine.* *β-Hygrine* (high boiling).

The occurrence of these alkaloids in coca leaves from various sources is as follows (the percentages of total alkaloids given are very uncertain, since the methods of estimation are in most cases different, and some of them are of doubtful accuracy) :

Commercial Coca Leaves

Geographical source.	Total alkaloids per cent.	Chief constituent.	Reference.
Java . .	1·0–2·5 (season 1908) 0·6–2·4 (season 1909) 1·22	Cinnamylcocaine .	de Jong, *Teysmannia,* 1910, **21,** 201 Hartwich, *Arch. Pharm.,* 1903, **241,** 617
Ceylon .	0·7–1·6	Cocaine	*Bull. Imp. Inst.* 1912, **10,** 37 ; and Hartwich, *loc. cit.*
Bolivia .	0·7–0·9	Cocaine	Hartwich, *loc. cit.*
Peru . .	Up to 1·00	Cocaine	Hartwich, *loc. cit.*

Coca leaves grown experimentally in India and examined by Howard contained 0·4 to 0·8 per cent. of alkaloid, largely cocaine. Small quantities of alkaloids have also been found in the leaves of *E. pulchrum* (South America), *E. monogynum* (India), *E. montanum*, *E. laurifolium*, *E. retusum*, *E. areolatum*, and *E. ovatum*.[1] de Jong has pointed out that the nature of the alkaloids in coca leaves varies with the age of the leaves, the youngest leaves being richest in cinnamylcocaine, whilst in the older leaves this is replaced by cocaine or truxilline.[2]

Estimation of Total Alkaloids. For the estimation of the total alkaloids of coca leaves the United States Pharmacopœia (8th Rev.) gave the following process :

Ten grammes of powdered leaves are mixed with 50 c.c. of a mixture of ether (4 vols.) with chloroform (1 vol.), and after ten minutes 2 c.c. of ammonia solution (sp. gr. 0·958 at 25°) are added, mixed with 3 c.c. of water, and the whole shaken frequently during one hour. The contents of the flask are now transferred to a small glass percolator plugged at the lower end with cotton wool and inserted in a separator containing 6 c.c. of *N*-sulphuric acid mixed with 20 c.c. of distilled water. When all the liquid has passed through, the powder in the percolator is packed in firmly with a glass rod, and the flask is rinsed out into the percolator with 10 c.c. of the ether-chloroform mixture, followed by other small portions of the same menstruum, using 50 c.c. in all. The separator is now shaken for one minute, the acid layer drawn off, and the extraction with diluted sulphuric acid (6 c.c. *N*-acid with 20 c.c. of water) repeated twice, using 10 c.c. each time. The combined acid liquids collected in a second separator are made alkaline with ammonia solution and shaken out with ether, using in succession 25, 20, and 15 c.c. The combined ethereal solutions are collected in a beaker, and the solvent allowed to evaporate completely over warm water. The residue is dissolved in 3 c.c. of ether, which is also allowed to evaporate. The residue is then dissolved in 4 c.c. of *N*/10 sulphuric acid and titrated back with *N*/50 potassium hydroxide solution, using cochineal or iodeosin as indicator. The percentage of ether-soluble alkaloids in the leaves is given by the formula $(4 - n/5)0 \cdot 3$, where n is the number of cubic centimetres of *N*/50 alkali used. The percentage should not be less than 0·5. A critical survey of methods

[1] *Kew Bulletin*, 1889, p. 8.
[2] *Rec. Trav. Chim.* 1906, **25**, 233.

for conducting the assay of coca leaves is given by Bierling, Pape and Viehover.[1]

The amount of cocaine in coca leaves cannot at present be accurately determined, but various methods are available by which an approximate estimate of the richness in cocaine of the total alkaloid obtained by the above method may be obtained.[2]

Estimation of Ecgonine. In view of the fact that much of the cocaine of commerce is not obtained directly from the leaves but from ecgonine obtained by the hydrolysis of the secondary alkaloids (*see* p. 95), a method for the estimation of ecgonine is of importance. Greshoff recommended the following process : The total alkaloids from 15 grm. of leaves are boiled for one hour in a reflux apparatus with thirty times their weight of dilute hydrochloric acid and an equal volume of water. When cold the solution is filtered and extracted twice in succession with its own volume of ether. The aqueous solution is then evaporated to dryness and the residual ecgonine hydrochloride weighed, after drying at 90°–95°.[3]

Cocaine, $C_{17}H_{21}O_4N$. The crude cocaine exported from Peru is prepared by extracting the finely ground leaves with dilute sulphuric acid. The acid extract is made alkaline with sodium carbonate, and the liberated alkaloids dissolved out with petroleum. From the latter they are re-extracted by dilute sulphuric acid and finally precipitated with sodium carbonate solution, the precipitate being washed with water, pressed, and dried for export. This material contains from 83 to 97 per cent. of cocaine. About 6,000 kilogrammes of this product are said to be exported per annum.[4] Most of the cocaine now made is prepared in Germany from Java coca leaves containing chiefly cinnamylcocaine which is extracted by mixing the finely ground leaves with 3 to 5 per cent. of slaked lime, adding sufficient water to form a stiff paste and treating this in a digester with kerosene, naphtha, or benzene. The separated oil is then agitated with sufficient dilute hydrochloric acid to convert the

[1] *Arch. Pharm.* 1910, **248**, 303.

[2] For such processes *see* Grandval and Lajoux, *Journ. Pharm.* 1893 [5], **28**, 102 ; Garsed, *Pharm. Journ.* 1903 [iv], **17**, 784. *Cf.* de Jong, *Rec. Trav. Chim.* 1906, **25**, 1.

[3] *Pharm. Weekbl.* 1907, **44**, 961. *Cf.* de Jong, *Rec. Trav. Chim.* 1906, **25**, 1 ; 1911, **30**, 204 ; *Pharm. Weekbl.* 1908, **45**, 42 ; and *Indische Mercuur*, 1923, **46**, 305 (*Chem. Soc. Abstr.* 1923 [ii], 798).

[4] *Chemist and Druggist*, 1912, **80**, 51. Purification of crude cocaine, *see* de Rosemont, *Bull. Sci. Pharm.* 1920, **27**, 359. Abstr. in *Chemist and Druggist*, 1920, p. 934.

alkaloid into the hydrochloride,[1] which can either be obtained as
such by evaporation, or converted into the base by adding sodium
carbonate.   For hydrolysis of this to ecgonine a solution of either
the mixed bases or their hydrochlorides is heated to the boiling-
point with dilute hydrochloric acid during one hour.   The mixture
is then poured into water to precipitate the insoluble truxillic and
other acids and the filtrate evaporated to dryness, the residue of
crude ecgonine hydrochloride being washed with alcohol.   The
ecgonine obtained by adding sodium carbonate and extracting with
dilute alcohol is digested with benzoic anhydride for one hour, the
excess of benzoic anhydride and the benzoic acid produced are
removed by ether, the benzoylecgonine remaining undissolved
together with unattacked ecgonine, which should not amount to
more than 20 per cent. of the quantity taken.   The two bases are
separated by washing with a small amount of water, in which
ecgonine is very soluble.   The purified benzoylecgonine is now
mixed with methyl iodide and a solution of sodium methoxide in
methyl alcohol, and the whole boiled for several hours, when cocaine
is quantitatively formed, and may be purified by crystallisation of
the hydrochloride.[2]   According to Merck the conversion of ecgonine
into cocaine may be accomplished in one operation by heating the
former with methyl iodide and benzoic anhydride under pressure.[3]
Einhorn and Willstätter [4] have found that the truxillines and
cinnamylcocaine can be converted into the methyl ester of ecgonine
by boiling their solutions in methyl alcohol (6 parts) containing
sulphuric acid (2 parts) for several hours, or by passing hydrogen
chloride into a solution of the alkaloids in methyl alcohol.   The
methyl ester so obtained can then be benzoylated to cocaine.

Cocaine crystallises from alcohol in monoclinic, four- to six-sided
prisms, m.p. 98°, and is volatile above 90°.   It is lævorotatory,
$[\alpha]_D - 15 \cdot 8°$, slightly soluble in cold water, readily soluble in alcohol
(1 in 5 at 25°), ether, benzene or light petroleum.   The aqueous
solution is alkaline to litmus, has a slightly bitter taste, and when
applied to the tongue produces a characteristic numbness.   The
ordinary salts of cocaine are crystalline.

[1] This process appears to be due to Bignon ; Guareschi.   *Einführung
in das Studium der Alkaloide*, p. 267, or *Jahresberichte*, 1885, 1714.   *Cf.*
de Jong, *Rec. Trav. Chim.* 1906, **25**, 311; 1923, **42**, 980.

[2] Liebermann and Giesel, *Berichte*, 1888, **21**, 3196.   *Cf.* Einhorn and
Klein, *ibid.* p. 3335.

[3] *Berichte*, 1885, **18**, 2953.

[4] *Ibid.* 1894, **27**, 1523.

COCAINE HYDROCHLORIDE, B.HCl, the salt chiefly used in medicine, crystallises from alcohol in short prisms, m.p. 200°–202° (*dry*), $[\alpha]_D - 71 \cdot 95°$ (in 2 per cent. aqueous solution), $- 67 \cdot 5°$ (in aqueous alcohol). It is readily soluble in water (1 in 0·4 at 25°), or alcohol (1 in 2·6 at 25°), but insoluble in ether or light petroleum. Two tests are in common use for gauging the freedom of the hydrochloride for use in medicine from the amorphous alkaloids, which may accompany or replace cocaine in the leaves. These are given in the British (1914) and United States (9th Rev.) Pharmacopœias in the following forms : The addition of 3 drops (0·1 c.c.) of $N/10$ potassium permanganate to 0·1 grm. of the salt in 5 c.c. of water containing 3 drops of dilute sulphuric acid (0·3 c.c.) (N-acid) gives a violet colour, which, if dust is excluded, does not fade in thirty minutes (*Brit. Pharm.*) indicating absence of cinnamylcocaine and certain other coca alkaloids. The figures in brackets are those given by the United States Pharmacopœia.

Maclagan's Test. (The figures in brackets in the following description are those prescribed in the United States Pharmacopœia, 9th Rev. for this test.) It consists in dissolving 0·06 grm (0·1 grm.) of the salt in 60 grm. of water (85 c.c.), adding 2 drops of 10 per cent. ammonia (0·2 c.c. of ammonia solution sp. gr. 0·958 at 25°), and stirring vigorously. After fifteen minutes the mixture should deposit a *crystalline* precipitate of free cocaine, the supernatant liquid being clear ; a milky appearance indicates the presence of amorphous alkaloids, especially isatropylcocaine.[1]

OTHER SALTS. The chromate, $B.H_2CrO_4.H_2O$, is sparingly soluble in water, and is precipitated as orange-yellow leaflets, m.p. 127°, when potassium chromate is added to an acid solution of the hydrochloride. The platinichloride, $B_2.H_2PtCl_6$, is micro-crystalline and sparingly soluble in water. Aqueous mercuric chloride gives with a solution of cocaine hydrochloride a bulky precipitate of the mercurichloride, $B.HCl.HgCl_2$, which may be crystallised from alcohol. The nitrate, periodide, $B.HI.I_2$, m.p. 161°, formate, m.p. 42°, lactate, oleate, stearate, benzoate and salicylate, which is triboluminescent, have also been used in medicine.

Detection. Cocaine may be detected by the peculiar sensation of numbness which it produces on the tongue. The following reactions are also useful : A cubic centimetre of a 3 per cent. solution of potassium permanganate gives a microcrystalline (rectangular

[1] *Cf.* Günther, *Ber. Pharm. Ges.* 1899, **9**, 38.

plates), violet precipitate with 0·01 grm. of the hydrochloride dissolved in two drops of water.[1] The alkaloid forms a colourless solution with sulphuric acid, which gives off benzoic acid on warming. The hydrochloride, heated with a little alcoholic potash, gives off an odour of methyl benzoate.

d-**Cocaine** (iso*Cocaine* d-*ψ*-*Cocaine*). A dextrorotatory isomeride of *l*-cocaine obtained from coca leaves by Liebermann and Giesel,[2] is now generally believed to have been produced by the action of alkalis on the *l*-cocaine contained in the leaves, but has since been prepared synthetically from *d*-ecgonine.[3] It differs considerably from natural *l*-cocaine in characters : the base melts at 46°, has $[\alpha]_D + 4\cdot5°$ (in water), $+ 42\cdot2°$ (in chloroform, Gottlieb) and the salts crystallise well and are less soluble than those of *l*-cocaine, B.HCl, m.p. 208°, $[\alpha]_D + 49\cdot8°$ (in water), B.HAuCl$_4$, m.p. 148°. The nitrate is sparingly soluble in water (1·5 in 100 at 20°). According to Willstätter and Bommer,[4] this isomeride is the *d*-form of methylbenzoyl-*ψ*-ecgonine (*cf.* p. 103).

dl-**Cocaine.** This was prepared by Willstätter and collaborators[4] from synthetic *dl*-ecgonine (*r*-*ψ*-ecgonine, Willstätter). It crystallises from light petroleum in hexagonal plates, m.p. 81·5°, yields a hydrochloride, m.p. 208°, and differs from natural *l*-cocaine in giving a sparingly soluble nitrate, m.p. 172°. The aurichloride, B.HAuCl$_4$. 2H$_2$O, is crystalline, m.p. 65°–70° or 164°–165° (*dry*) (*cf.* p. 104).

When heated with mineral acids *l*-cocaine is hydrolysed into *l*-ecgonine (*see* p. 103), benzoic acid, and methyl alcohol,[5] and a similar change takes place with baryta water. If the alkaloid is boiled with water, methyl alcohol alone is split off, and a new base, benzoyl-*l*-ecgonine (p. 102), is produced,[6] which in turn by hydrolysis with acids or alkalis yields ecgonine and benzoic acid.

$$C_{17}H_{21}O_4N + H_2O \rightarrow CH_3OH + C_{16}H_{19}O_4N + H_2O \rightarrow$$
Cocaine   *Benzoyl*-l-*ecgonine*

$$C_9H_{15}O_3N + C_6H_5.COOH$$
Ecgonine
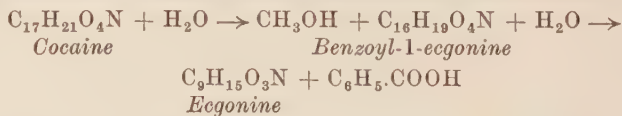
Cocaine is, therefore, methylbenzoylecgonine.

l-**Cinnamylcocaine**, $C_{19}H_{23}O_4N$. This alkaloid was isolated by

[1] *Cf.* Seiter, *Amer. Journ. Pharm.* 1911, **83**, 195, 265 ; Hankin, *Analyst*, 1911, **35**, 2.

[2] *Berichte*, 1890, **23**, 508, 926.

[3] Einhorn and Marquardt, *ibid.* 1890, **23**, 468, 981.

[4] *Annalen*, 1903, **326**, 42 ; 1921, **422**, 15.

[5] Lossen, *ibid.* 1865, **133**, 351.

[6] Paul, *Pharm. Journ.* 1887–88 [iii], **18**, 781 ; Einhorn, *Berichte*, 1888, **21**, 47.

Giesel [1] from Java coca leaves after it had been prepared synthetically by Liebermann.[2]

It is practically insoluble in water, but easily soluble in organic solvents. It crystallises best from benzene or light petroleum in rosettes of needles, m.p. 121°, $[\alpha]_D - 4\cdot7°$ in chloroform. The hydrochloride, $B.HCl.2H_2O$, forms long shining, somewhat flattened needles, m.p. 176° (*dry*), from water. The platinichloride, m.p. 217°, as precipitated, is amorphous, but crystallises on standing. The aurichloride forms yellow needles, m.p. 156°. When warmed with hydrochloric acid the base is hydrolysed, furnishing *l*-ecgonine, cinnamic acid, and methyl alcohol. The synthesis of the alkaloid was effected by heating ecgonine at 100° with cinnamic anhydride and methylating the resulting cinnamoylecgonine (colourless needles, m.p. 216°).

The isomeric *d*-CINNAMYLCOCAINE was prepared by Einhorn and Deckers,[3] by the action of cinnamoyl chloride at 150°–160° on *d*-ψ-ecgonine methyl ester. It crystallises in prisms, m.p. 68°, $[\alpha]_D + 2°$ in alcohol. The hydrochloride, $B.HCl$, forms needles, m.p. 186° ; the platinichloride, needles, m.p. 208° ; and the aurichloride, orange needles, m.p. 164°.

Truxillines, $C_{38}H_{46}O_8N_2$. In 1887, Hesse isolated from Peruvian coca leaves an amorphous alkaloid which he named cocamine ; [4] a year later Liebermann [5] examined this material, and by fractionation of its solutions by addition of petroleum proved it to be a mixture of at least two isomeric bases, which he named α- and β-truxillines. The pure alkaloids have not been obtained from coca leaves owing to the difficulty of separating them, but each has been prepared synthetically.[6]

α-TRUXILLINE (*Cocamine, γ-isatropylcocaine*). An amorphous white powder, m.p. 80°, easily soluble except in light petroleum and water. Solutions of the base are lævorotatory and possess a bitter taste. When warmed with hydrochloric acid the base undergoes hydrolysis with the production of *l*-ecgonine, methyl alcohol, and α-truxillic acid (*γ-isatropic acid*), according to the following equation :

$$C_{38}H_{46}O_8N_2 + 4H_2O = (C_9H_8O_2)_2 + 2CH_3OH + 2C_9H_{15}O_3N$$
α-*Truxilline*   α-*Truxillic acid*   1-*Ecgonine*
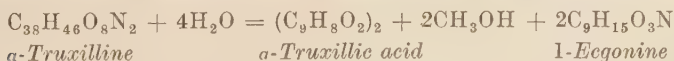
[1] *Berichte*, 1889, **22**, 2661.
[2] *Ibid.* 1888, **21**, 3372.
[3] *Ibid.* 1891, **24**, 7.
[4] *Pharm. Zeit.* 1887, 407, 668 ; *Berichte*, 1889, **22**, 665.
[5] *Berichte*, 1888, **21**, 2342.
[6] Liebermann and Drory, *ibid.* 1889, **22**, 682.

The synthesis of the alkaloid was accomplished by the action of α-truxillic anhydride on *l*-ecgonine and methylation of the resulting α-truxilloylecgonine.

β-Truxilline (iso*Cocamine*, δ-*isatropylcocaine*). This base sinters at 45°, and decomposes above 120°, $[\alpha]_D - 29\cdot3°$. It undergoes hydrolysis, furnishing β-truxillic acid (δ-isatropic acid) together with ecgonine and methyl alcohol. It also has been synthesised by Liebermann and Drory.[1] Much work [2] has been done on the truxillic acids, but considerations of space and the fact that it is only of secondary importance in connection with the coca alkaloids, preclude a full account of it being given here.

Methylcocaine (*Ethylbenzoylecgonine*). This base was isolated by Günther [3] from commercial cocaine, by dissolving the latter in an alcoholic solution of hydrogen chloride and fractional precipitation with ether, the new alkaloid being precipitated last. It melts at 110°, and possesses the same physiological properties as cocaine ; further, it yields an aurichloride and a platinichloride closely resembling the corresponding salts of that base. It is probable that it results from the use of ethyl alcohol as a solvent in the commercial preparation of cocaine from ecgonine, but it is stated by Günther to be isomeric, not identical, with cocaethyline (ethylbenzoylecgonine) prepared synthetically by esterifying benzoylecgonine with ethyl alcohol.[4]

Benzoylecgonine, $C_9H_{14}(CO.C_6H_5)O_3N$. This acyl ester of ecgonine was isolated about the same time by Skraup in Austria and Merck in Germany from Peruvian coca leaves, and was subsequently prepared by Paul [5] by the action of water on cocaine (*see* p. 100), and later synthesised by Liebermann and Giesel [6] by the action of benzoic anhydride on ecgonine.

It crystallises from water with $4H_2O$ in needles, m.p. 86° or 195° (*dry*), $[\alpha]_D - 63\cdot3°$, and dissolves readily in alkaline liquids, forming salts. The aurichloride forms yellow shining plates. When

[1] Liebermann and Drory, *Berichte*, 1889, **22**, 682.
[2] Liebermann and co-workers, *ibid.* 1888, **21**, 2342 ; 1889, **22**, 124, 130, 680, 782, 2240 ; 1890, **23**, 2516 ; Rüber, *ibid.* 1902, **35**, 2411, 2908 ; de Jong, *Proc. K. Akad. Weten. Amst.* 1918, **20**, 590 ; 1920, **22**, 509 ; 1922, **25**, 175 ; *Berichte*, 1922, **55**, 463 (summary of de Jong's work); Stobbe, *Berichte*, 1919, **52**, 1021 ; 1923, **56**, 676 ; Stoermer and co-workers, *ibid.* 1919, **52**, 1255 ; 1920, **53**, 497 ; 1921, **54**, 77, 85, 96 ; 1922, **55**, 1860 ; 1923, **56**, 1683 ; 1924, **57**, 15.
[3] *Chem. Soc. Abstr.* 1899 [i], 963.
[4] Merck, *Berichte*, 1885, **18**, 2954 ; Einhorn, *ibid.* 1888, **21**, 48.
[5] *Pharm. Journ.* 1887–88 [iii], **18**, 781.
[6] *Berichte*, 1888, **21**, 3196.

boiled with dilute hydrochloric acid, it is hydrolysed into ecgonine and benzoic acid, and on esterification with methyl alcohol furnishes cocaine, and with other aliphatic alcohols yields a series of homologues of cocaine : of these the ethyl ester (cocaethyline), m.p. 108°–109°, the propyl ester (cocapropyline), m.p. 78°–79·5°, and the *iso*butyl ester, m.p. 61°–62°, among others, have been prepared.

l-ECGONINE, $C_9H_{15}O_3N.H_2O$. This substance was first obtained by Lossen in 1862 [1] as the final basic hydrolytic product of the action of acids on cocaine, and is obtainable in like manner from several of the alkaloids occurring with cocaine (*see above*). It crystallises from dry alcohol in monoclinic prisms, m.p. 198° (*decomp.*), 205° (*dry*), is soluble in water, sparingly so in alcohol, insoluble in most organic liquids ; the solutions are lævorotatory, $[\alpha]_D - 45\cdot4°$. Ecgonine forms salts both with bases and acids ; the hydrochloride crystallises in rhombs, m.p. 246° ; the aurichloride, $B.HAuCl_4$, forms yellow prisms ; and the platinichloride, red needles, m.p. 226° (*dry*).

It is readily esterified in presence of hydrogen chloride, and in this way various alkylecgonines have been prepared. The most important of these is the methyl ester, which was obtained by Einhorn and Klein in 1888 in the form of the hydrochloride crystallising, with $1H_2O$, in colourless prisms, m.p. 212° (*decomp.*), b.p. 177°/15 mm. When benzoylated this furnishes cocaine. Ecgonine also reacts with acid chlorides and anhydrides to form acyl derivatives : thus by the action of benzoic anhydride, benzoylecgonine (*see* p. 102) is produced, and cinnamoyl-, *iso*valeroyl-, anisoyl-, and truxilloyl-ecgonines have been similarly prepared ; these, in turn, by esterification with methyl alcohol, furnish the corresponding cocaines.

d-ECGONINE (d-*ψ*-*Ecgonine*). This isomeride of ecgonine was prepared by Einhorn and Marquardt [2] by the action of potassium hydroxide solution on ecgonine, and is formed when the cocaines are hydrolysed by alkalis. It crystallises from dry alcohol in tablets, for which m.p. 254°, 257°, and 264° have been recorded : the hydrochloride forms monoclinic prisms, m.p. 236°, $\alpha_D = + 1\cdot6$ (c. $= 4\cdot4$; l $=$ 2dcm.) ; the aurichloride, $B.HAuCl_4$, has m.p. 220° (*decomp.*). It forms a series of esters like those yielded by *l*-ecgonine, and from it *d*-cocaine (*methylbenzoyl-d-ψ-ecgonine*) has been prepared (*see* p. 100).

dl-ECGONINE (r-*ψ*-*ecgonine*). This was prepared by Willstätter

[1] *Annalen*, 1865, **133**, 351.
[2] *Berichte*, 1890, **23**, 468, 981. *Cf.* Liebermann and Giesel, p. 511.

and Bode by the reduction of tropineonecarboxylic acid.[1] It forms rhombic crystals, m.p. 251° (*decomp.*), and yields a hydrochloride, $B.HCl.\frac{1}{2}H_2O$, crystallising in slender needles, m.p. 149° (*dry, decomp.*), and an aurichloride, glistening needles, m.p. 213°. On benzoylation and methylation it yields *dl*-cocaine (p. 100). According to Willstätter and Bommer,[2] *d*-ecgonine has the same relation to natural *l*-ecgonine as ψ-tropine has to tropine, and they propose to name the *d*- and *dl*-bases *d*-ψ-ecgonine and *dl*-ψ-ecgonine respectively.

Constitution of Ecgonine, $C_9H_{15}O_3N$. The facts recorded above furnish evidence of the existence of a hydroxyl and a carboxyl group in the molecule of ecgonine. Einhorn observed [3] that dehydrating agents remove the elements of a molecule of water from ecgonine, forming anhydroecgonine, $C_9H_{13}O_2N$, which crystallises from alcohol in needles, m.p. 235°, is unsaturated, combining with two atoms of bromine, and still contains the —COOH group of the parent base since it esterifies alcohols. Ethyl anhydroecgonine has been found in residues obtained in working up the secondary alkaloids of coca leaves,[4] and is probably formed in this process. It has b.p. 130°–132°/11 mm., $[\alpha]_D - 51°$ 33', and yields an aurichloride, m.p. 124°. When heated with hydrochloric acid at 280°, it loses a molecule of carbon dioxide with the formation of tropidine (*see* p. 74), whence it appears that anhydroecgonine and ecgonine are carboxylic acids of tropidine and hydroxytropidine [5] respectively. The close relationship of ecgonine to tropine is brought out even more clearly by its products of oxidation, which when chromic anhydride in acetic acid is the agent used, are [6]: tropinone, $C_8H_{13}ON$ (p. 75), tropinic acid, $C_8H_{13}O_4N$ (p. 76), and ecgoninic acid, $C_7H_{11}O_3N$.

Ecgoninic acid crystallises from benzene in colourless needles, m.p. 93°, and has been shown by Willstätter and Bode to be *N*-methylpyrrolidone-2-acetic acid,[7] and this has been confirmed by Willstätter and Hollander's [8] synthesis of the acid.

When ecgonine is treated with permanganate in acid solution a new base, norecgonine, $C_8H_{13}O_3N$, is the principal product. It stands in the same relation to ecgonine as the similarly produced

[1] *Berichte*, 1901, **34**, 1457.
[2] *Annalen*, 1921, **422**, 15.
[3] *Berichte*, 1887, **20**, 1221.
[4] Liebermann, *ibid.* 1907, **40**, 3602.
[5] Einhorn, *ibid.* 1890, **23**, 1338.
[6] Liebermann, *ibid.* 1890, **23**, 2518 ; 1891, **24**, 606 ; Willstätter and Müller, 1898, **31**, 178.
[7] *Ibid.* 1901, **34**, 519.
[8] *Ibid.* p. 1818.

tropigenine does to tropine (p. 76), and, like its analogue, is a secondary base, produced by the oxidation of a methyl group attached to nitrogen. It crystallises in long needles, m.p. 233°, is very soluble in water, and gives a characteristic aurichloride, m.p. 211°, crystallising in yellow needles.[1] Similarly on degradation by Hofmann's reaction,[2] anhydroecgonine gives rise to *δ-cyclo*-heptatrienecarboxylic acid, $C_8H_8O_2$, whilst tropidine, it will be remembered, yields the corresponding cycloheptatriene (p. 79).

The close relationship shown by these reactions to exist between ecgonine and tropine is evident from the following diagrammatic summary :
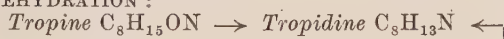
DEHYDRATION :
  Tropine $C_8H_{15}ON$ $\longrightarrow$ *Tropidine* $C_8H_{13}N$ $\longleftarrow$
DEHYDRATION AND DECARBOXYLATION :
  Ecgonine $C_9H_{15}O_3N$ $\longrightarrow$ *Anhydroecgonine* $C_9H_{13}O_2N$
OXIDATION : (a) *Chromic acid*
  Tropine $C_8H_{15}ON$ $\longrightarrow$ *Tropinone* $\longrightarrow$ *Tropinic acid* $\longrightarrow$ *Ecgoninic acid*
  Ecgonine $C_9H_{15}O_3N$ $C_8H_{13}ON$ $C_8H_{13}O_4N$ $C_7H_{11}O_3N$
  (b) *Permanganate*
  Tropine $C_8H_{15}ON$ $\longrightarrow$ *Tropigenine* $C_7H_{13}ON$
  Ecgonine $C_9H_{15}O_3N$ $\longrightarrow$ *Norecgonine* $C_8H_{13}O_3N$
EXHAUSTIVE METHYLATION :
  Tropidine $C_8H_{13}N$ $\longrightarrow$ *Tropilidene* C_7H_8 (*δ-cyclo*Heptatriene)
  Anhydroecgonine $C_9H_{13}O_2N \longrightarrow$ δ-cyclo*Heptatrienecarboxylic acid* [2]
                              $C_8H_8O_2$
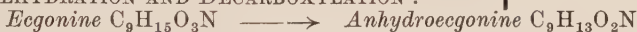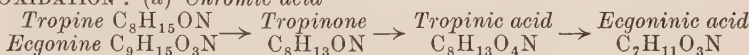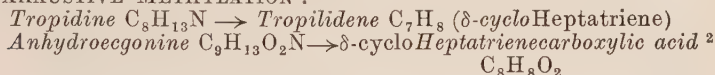
It will be seen that ecgonine and its derivatives differ from tropine and its derivatives throughout by CO_2, so that the former probably stands to the latter in the relation of a carboxylic acid, and hence the formulæ assigned at various times to tropine by Ladenburg, Merling and Willstätter, have been suitably modified to represent ecgonine : thus the following two formulæ are based on the tropine formulæ of Ladenburg and Merling respectively :
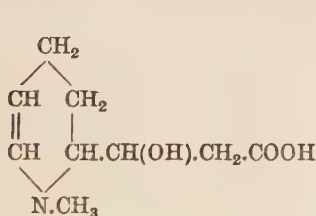
| *Ecgonine* | *Ecgonine* |
| (Einhorn after Ladenburg) | (Einhorn and Tahara after Merling) |
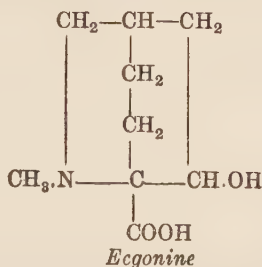
[1] Einhorn, *Berichte*, 1888, **21**, 3031.
[2] Einhorn and Friedländer, *ibid.* 1893, **26**, 1482. *Cf.* Willstätter and Müller, *ibid.* 1898, **31**, 2498, 2655.

There are two possible formulæ for ecgonine derivable from Willstätter's representation of tropine (p. 77) which may be written thus [1] :

$$
\begin{array}{ccc}
\text{CH}_2\text{—CH}\text{———}\text{CH}_2 \\
\quad\quad |\quad\quad\quad | \\
\quad\quad \text{N.CH}_3\quad \text{CHOH} \\
\quad\quad |\quad\quad\quad | \\
\text{CH}_2\text{—CH}\text{———}\text{CH}_2 \\
\textit{Tropine}
\end{array}
\qquad
\begin{array}{ccc}
\text{CH}_2\text{—CH}\text{———}\text{CH.OH} \\
\quad\quad |\quad\quad\quad | \\
\quad\quad \text{N.CH}_3\quad \text{CH.COOH} \\
\quad\quad |\quad\quad\quad | \\
\text{CH}_2\text{—CH}\text{———}\text{CH}_2 \\
(\textsc{i})
\end{array}
\quad \text{or} \quad
\begin{array}{ccc}
\text{CH}_2\text{—CH}\text{———}\text{CH.COOH} \\
\quad\quad |\quad\quad\quad | \\
\quad\quad \text{N.CH}_3\quad \text{CHOH} \\
\quad\quad |\quad\quad\quad | \\
\text{CH}_2\text{—CH}\text{———}\text{CH}_2 \\
(\textsc{ii})
\end{array}
$$
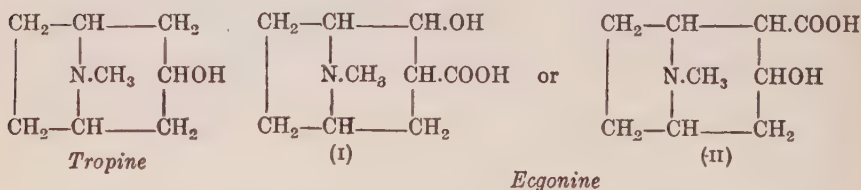
<center>Ecgonine</center>

The position assigned to the hydroxyl group in formula II explains (1) the ease with which ecgonine loses a molecule of water, forming anhydroecgonine, this change taking place between the —CHOH group and the neighbouring —CH$_2$ group ; and (2) Willstätter and Müller's observation [2] that an unstable β-ketonic acid precedes the formation of tropinone, when ecgonine is oxidised by chromic acid. Further, when ecgonine ethyl ester is reduced by sodium in alcohol, it yields hydroecgonidine, C$_9$H$_{15}$O$_2$N, and the amide corresponding to this on oxidation with sodium hypobromite yields *iso*tropylamine, isomeric with tropylamine (or *pseudo*tropylamine) obtained by the reduction of tropinoneoxime, but not identical with either ; it follows, therefore, that the amino group in the latter amines must occupy a position different from that in the former, thus :

$$
\begin{array}{ccc}
\text{CH}_2\text{—CH}\text{———}\text{CH}_2 \\
\quad\quad |\quad\quad\quad | \\
\quad\quad \text{N.CH}_3\quad \text{C:NOH} \\
\quad\quad |\quad\quad\quad | \\
\text{CH}_2\text{—CH}\text{———}\text{CH}_2 \\
\textit{Tropinoneoxime}
\end{array}
\qquad
\begin{array}{ccc}
\text{CH}_2\text{—CH}\text{———}\text{CH}_2 \\
\quad\quad |\quad\quad\quad | \\
\quad\quad \text{N.CH}_3\quad \text{CH.NH}_2 \\
\quad\quad |\quad\quad\quad | \\
\text{CH}_2\text{—CH}\text{———}\text{CH}_2 \\
\textit{Tropylamine} \text{ and pseudo}\textit{Tropylamine}
\end{array}
$$

$$
\begin{array}{ccc}
\text{CH}_2\text{—CH}\text{———}\text{CH.CONH}_2 \\
\quad\quad |\quad\quad\quad | \\
\quad\quad \text{N.CH}_3\quad \text{CH}_2 \\
\quad\quad |\quad\quad\quad | \\
\text{CH}_2\text{—CH}\text{———}\text{CH}_2 \\
\textit{Hydroecgonidineamide}
\end{array}
\qquad
\begin{array}{ccc}
\text{CH}_2\text{—CH}\text{———}\text{CH.NH}_2 \\
\quad\quad |\quad\quad\quad | \\
\quad\quad \text{N.CH}_3\quad \text{CH}_2 \\
\quad\quad |\quad\quad\quad | \\
\text{CH}_2\text{—CH}\text{———}\text{CH}_2 \\
\text{iso}\textit{Tropylamine}
\end{array}
$$
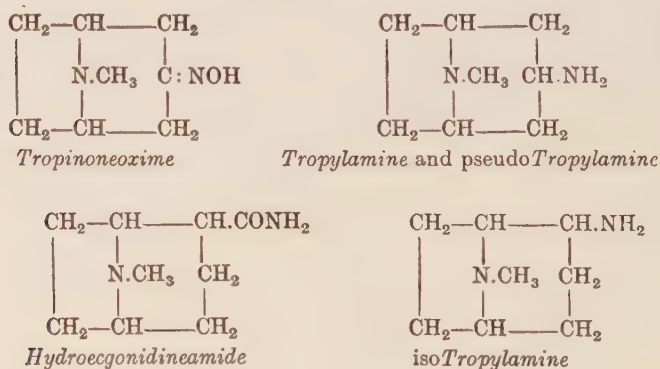
Accepting this view of the constitution of ecgonine, the formulæ of its derivatives and of cocaine must be written as follows :

[1] Willstätter, *Berichte*, 1897, **30**, 2679 ; 1898, **31**, 1534, 2655.
[2] *Ibid.* 1898, **31**, 1212, 2655.

$$CH_2-CH\underline{\quad\quad}CH.COOH$$
$$\mid\qquad\qquad\mid$$
$$N.CH_3\quad CHOH \qquad \text{by dehydration} \longrightarrow$$
$$\mid\qquad\qquad\mid$$
$$CH_2-CH\underline{\quad\quad}CH_2$$
Ecgonine

$$CH_2-CH\underline{\quad\quad}CH.COOH \qquad\qquad CH_2-CH\underline{\quad\quad}CH.COOH$$
$$\mid\qquad\qquad\mid\qquad\quad\text{reduction}\qquad\mid\qquad\qquad\mid$$
$$\longrightarrow\quad N.CH_3\quad CH.OH \qquad \text{by Na} \qquad N.CH_3\quad CH_2$$
$$\mid\qquad\qquad\parallel\qquad\longrightarrow\qquad\mid\qquad\qquad\mid$$
$$CH_2-CH\underline{\quad\quad}CH.H \qquad\qquad CH_2-CH\underline{\quad\quad}CH_2$$
Anhydroecgonine   *Hydroecgonidine*

Oxidation by $KMNO_4$ By methylation and benzoylation

$$CH_2-CH-CH.COOH \qquad\qquad CH_2-CH\underline{\quad\quad}CH.CO_2.CH_3$$
$$\mid\qquad\quad\mid\qquad\qquad\qquad\quad\mid\qquad\qquad\mid$$
$$NH\quad CH.OH \qquad\qquad\qquad N.CH_3\quad CH\ OC_7H_5O$$
$$\mid\qquad\quad\mid\qquad\qquad\qquad\quad\mid\qquad\qquad\mid$$
$$CH_2-CH-CH_2 \qquad\qquad\qquad CH_2-CH\underline{\quad\quad}CH_2$$
Norecgonine   *Cocaine*
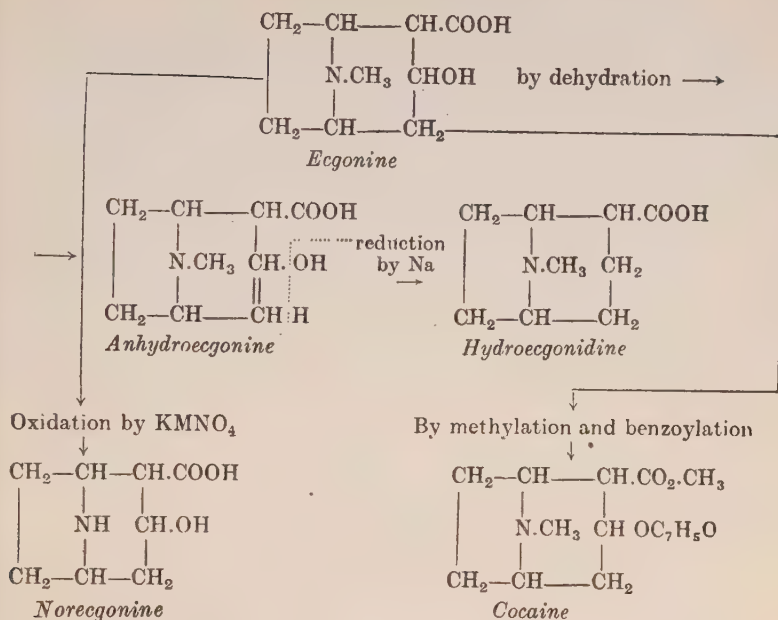
Willstätter and Bommer [1] made it clear in 1921 that the synthesis of ecgonine and consequently of cocaine had not been effected, a point on which there had been some confusion owing to the fact that the alkali-labile natural ecgonine had been regarded as the optical antipode of the alkali-stable so-called *d*-ecgonine, whilst the optically inactive isomeride synthesised by Willstätter and Bode has been regarded as the *dl*-form of natural ecgonine. The view taken by the former authors is that the alkali-stable form (*d*-ecgonine) is a *ψ*-ecgonine having the same relation to natural *l*-ecgonine as tropine has to *ψ*-tropine (p. 109), whilst the inactive form is one of four possible racemates. [2]

Willstätter and Bode [3] converted tropinone into *ψ*-ecgonine, by treating sodium tropinone with carbon dioxide and sodium when it yielded sodium tropinonecarboxylate. This on reduction with sodium in alcohol gave some *dl-ψ*-ecgonine (*see* p. 103). This on esterification with methyl alcohol and benzoylation yielded a *dl*-cocaine (*see* p. 100). A somewhat simpler synthesis of *ψ*-ecgonine has since been achieved by Willstätter and Bommer, and reference

[1] *Annalen*, 1921, **422**, 1, 15.
[2] Compare, however, Gadamer and John, *Arch. Pharm.* 1921, **259**, 227, 241.
[3] *Berichte*, 1901, **34**, 1457.

is made on p. 83 to other processes, some of which have been protected by patents. These improvements having enabled the preparation of methyl tropinonecarboxylate to be undertaken on a large scale, Willstätter, Wolfes and Mäder [1] have re-investigated the reduction of this ester and found that both dl-ψ-ecgonine and dl-ecgonine methyl esters are formed, and from these the corresponding dl-cocaines were obtained by benzoylation. dl-Cocaine was resolved into its optically active components by crystallisation of the hydrogen-d-tartrate to give the l-base (natural cocaine) and of the hydrogen l-tartrate to give the d-base. dl-ψ-Cocaine could not be resolved directly, but its components were obtained by resolving dl-ψ-ecgonine methyl ester and benzoylating the two forms.

α-ECGONINE is the name given to a base, isomeric with ecgonine, and prepared by Willstätter [2] by the addition of hydrocyanic acid to tropinone, and hydrolysis of the cyanohydrin so formed :

```
CH2—CH——CH2                CH2—CH——CH2
 |      |     |              |      |     |   OH
 |   N.CH3   CO             |   N.CH3   C
 |      |     |              |      |     |   COOH
CH2—CH——CH2                CH2—CH——CH2
    Tropinone                    a-Ecgonine
```
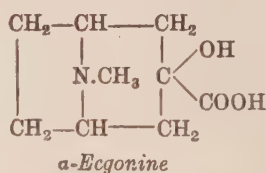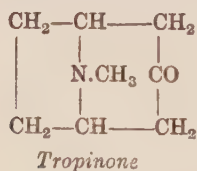
It occurs in brilliant snow-white crystals, m.p. 305° (*decomp.*), and is readily soluble in water or aqueous alcohol. The benzoyl derivative, m.p. 209°, is crystalline, and on methylation gives α-cocaine, a base crystallising in prisms, m.p. 87°, and yielding an aurichloride, m.p. 222° (*decomp.*), crystallising in leaflets. It is bitter to the taste, but has no local anæsthetic action.

Tropacocaine (*Benzoyl*pseudo*tropëine*), $C_{15}H_{19}O_2N$, was discovered by Giesel [3] in Java coca leaves, and has since been found in Peruvian coca.[4] It crystallises in needles, m.p. 49°, is insoluble in water, but soluble in alcohol, ether, or dilute ammonia, and is generally prepared by benzoylating *pseudo*tropine made from tropine and purified by recrystallisation of the hydrochloride. Its alcoholic solution is strongly alkaline and optically inactive. The hydrochloride forms needles, m.p. 283° (*decomp.*), and the hydrobromide

[1] *Annalen*, 1923, **434,** 111. *Cf.* Brit. Pat. 214,917.
[2] *Berichte*, 1896, **29,** 2216.
[3] *Ibid.* 1891, **24,** 2336.
[4] Hesse, *Journ. prakt. Chem.* 1902 [ii], **66,** 401.

leaflets. The aurichloride separates in minute yellow needles, m.p. 208°, from hot aqueous solutions; the picrate has m.p. 238°–239°.

When heated with hydrochloric acid or baryta water the alkaloid undergoes hydrolysis with the formation of benzoic acid and *pseudo*-tropine,[1] thus :

$$C_{15}H_{19}O_2N + H_2O = C_6H_5COOH + C_8H_{15}ON$$
*Benzoyl*pseudo*tropëine Benzoic acid pseudoTropine*
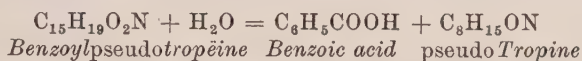
*pseudo*TROPINE, $C_8H_{15}ON$. This base is isomeric with tropine (p. 72), and since it furnishes on oxidation the same products as the latter, and, like it, gives tropidine when dehydrated, it is regarded as a stereoisomeride. It crystallises in colourless tablets or prisms, m.p. 108°, b.p. 240°, is miscible with water, ether, or alcohol, is strongly alkaline in reaction, and optically inactive. The hydrochloride forms hygroscopic needles; the aurichloride crystallises in brilliant yellow plates, m.p. 225° (*decomp.*). *pseudo* Tropine esterifies with organic acids, furnishing a series of derivatives, which from their analogy with the tropëines have been called *pseudo*tropëines, but, unlike the former, exert little or no mydriatic action.

*Mandelyl*pseudo*tropëine* (*pseudo*homatropine), $C_{16}H_{21}O_3N$, is a thick uncrystallisable oil.

*Tropyl*pseudo*tropëine*, $C_{17}H_{23}O_3N$, crystallises in colourless needles, m.p. 86°.

Tropine and *pseudo*tropine are mutually convertible; thus each alone gives tropinone on oxidation in chromic acid, and this in turn on reduction yields a mixture of tropine and ψ-tropine, which can be separated by means of the picrates, that of ψ-tropine being the more soluble in water.[2] By the action of sodium amyloxide on tropine, Willstätter has shown that *pseudo*tropine is produced,[3] and this has been confirmed by Barrowcliff and Tutin,[4] who also support Willstätter's view that both bases are internally compensated, the relation being that of *cis-trans*-isomerism.[5] The synthesis of ψ-tropine has been described already (p. 81). Tröger and Schwarzenberg[6] have recently obtained a new base isomeric with tropine and ψ-tropine from coca leaves.

[1] Liebermann, *Berichte*, 1891, **24,** 2338.
[2] Willstätter, *ibid.* 1900, **33,** 1167. *Cf.* however, Ladenburg, *ibid.* 1902, **35,** 1159.
[3] *Ibid.* 1896, **29,** 936.
[4] *Trans. Chem. Soc.* 1909, **95,** 1970.
[5] *Cf.* Willstätter, *Annalen*, 1901, **317,** 204 ; 1903, **326,** 1 ; 1921, **422,** 15.
[6] *Arch. Pharm.* 1921, **259,** 207.

HYGRINES

This group of coca alkaloids was discovered by Lossen [1] in an ethereal extract of a slightly alkaline percolate of Peruvian coca leaves. Liebermann and his pupils [2] reinvestigated Lossen's supposed homogeneous base, and observed that by distillation under reduced pressure it could be separated into two fractions.

Hygrine, $C_8H_{15}ON$, b.p. $92°$–$94°/20$ mm., $111°$–$113°/50$ mm., or $193°$–$195°/760$ mm., $D_4^{17°}$ 0.940, $[x]_D$ — $1.3°$, is a colourless, strongly alkaline liquid, which absorbs carbon dioxide from the air and decomposes on exposure to light. It forms an aurichloride and a characteristic picrate, the latter crystallising in yellow needles, m.p. $158°$, dl-form $176°$. On oxidation by chromic acid hygrine yields hygric acid, $C_6H_{11}O_2N$, which heated alone or with strong sulphuric acid loses carbon dioxide, giving N-methylpyrrolidine, $C_5H_{11}N$. Both hygric acid and hygrine are tertiary amines, and hygrine gives a crystalline oxime, m.p. $116°$–$120°$ (dl-form, m.p. $125°$).

Hygric acid has been synthesised by Willstätter by the following series of reactions [3]: Ethylbromopropylmalonate, $CH_2Br.CH_2.CH_2.CH(CO_2Et)_2$, obtained by condensation of trimethylene bromide with ethyl sodiomalonate, on bromination yielded ethyl $\alpha\delta$-dibromopropylmalonate, $CH_2Br.CH_2.CH_2.CBr(CO_2C_2H_5)_2$. This reacts with ammonia and amines, forming cyclic amides derived from pyrrolidine and piperidine ; thus with methylamine the chief product of the reaction is a substance of the formula (I), with a small quantity of ethyl N-methylpyrrolidine-2 : 2-dicarboxylate (II).

(I)   (II)

The latter, on hydrolysis, loses ethyl alcohol and carbon dioxide, forming hygric acid, which is, therefore, N-methylpyrrolidine-2-carboxylic acid.

On the basis of these results, Willstätter suggested that of the

[1] *Annalen*, 1862, **121**, 374.
[2] *Berichte*, 1889, **22**, 675 ; 1891, **24**, 407 ; 1893, **26**, 851 ; 1895, **28**, 578 ; 1896, **29**, 2050 ; 1897, **30**, 1113.
[3] *Ibid.* 1900, **33**, 1160 ; *Annalen*, 1903, **326**, 91.

two formulæ available for the representation of hygrine, the second was the more probable :

$$\text{(I)} \quad CH_2{\Large\langle}\begin{array}{l}CH_2.NMe\\[2pt]\;|\\[2pt]CH_2.CH.CO.Et\end{array} \qquad \text{(II)} \quad CH_2{\Large\langle}\begin{array}{l}CH_2.NMe\\[2pt]\;|\\[2pt]CH_2.CH.CH_2.COMe\end{array}$$

and this has been confirmed by K. Hess's synthesis [1] of racemic hygrine. The secondary alcohols corresponding to the ketones represented by the two formulæ just given, were prepared (1) by treating magnesium pyrryl bromide with propionyl chloride, reducing the 2-propionylpyrrole so formed and methylating the resulting 2-propionylpyrrolidine : the product is represented by formula III ; (2) by the addition of propylene oxide to magnesium pyrryl bromide, reduction of the product with hydrogen in presence of spongy platinum and methylation of the resulting pyrrolidyl*iso*propyl alcohol, giving a product represented by formula IV

$$CH_2{\Large\langle}\begin{array}{l}CH_2.NMe\\[2pt]\;|\\[2pt]CH_2.CH.CHEt.OH\end{array} \qquad\qquad CH_2{\Large\langle}\begin{array}{l}CH_2.NMe\\[2pt]\;|\\[2pt]CH_2.CH.CH_2.CHMe.OH\end{array}$$

$$\qquad\qquad\text{III}\qquad\qquad\qquad\qquad\qquad\qquad\text{IV}$$

When the final methylation of either product is effected with formaldehyde, oxidation of the secondary alcohol group occurs simultaneously in each case, and of the two resulting ketones that from product IV proves to be racemic hygrine, which must, therefore, have formula II given above.

β-**Hygrine,** $C_{14}H_{24}ON_2$. This, the second fraction of Lossen's hygrine,[2] decomposes when distilled under ordinary pressure, but boils at 215° under 50 mm. pressure, and has specific gravity 0·982 at 18°. It gives an aurichloride, $C_{14}H_{24}ON_2.2HAuCl_4$, and forms a colourless crystalline dimethiodide. When oxidised by chromic acid, it yields a small quantity of hygric acid.

Cuscohygrine, $C_{13}H_{24}ON_2$. This third hygrine, first recognised by Liebermann and Cybulski [3] in " Cusco " leaves, whose botanical origin is unknown, boils at 185° under 32 mm. pressure, has specific gravity 0·9767 at 17°, and is optically inactive. It is miscible with water, and forms a crystalline hydrate, $C_{13}H_{24}ON_2.3\frac{1}{2}H_2O$, m.p. 40°, and with carbon dioxide forms an unstable carbonate. It yields an oxime, m.p. 53°–54°. The alkaloid forms crystalline salts with acids, has been shown to contain two tertiary nitrogen atoms, and

[1] *Berichte*, 1913, **46**, 3113, 4104.
[2] *Ibid.* 1889, **22**, 675 ; 1895, **28**, 580.
[3] *Ibid.* 1895, **28**, 578.

yields hygric acid on oxidation with chromic acid. Liebermann assigned to it the following formula, which Hess and his co-workers [1] modified as shown, chiefly on the ground that a substance having formula I contains two active methylene groups, and should form

$$CH_2{-}CH_2$$
$$CH_2 \quad CH{-}CH_2{-}CO - CH_2{-}CH \quad CH_2 \qquad [\ ]{-}CH(COMe){-}[\ ]$$
$$N.CH_3 \qquad\qquad\qquad N.CH_3 \qquad NMe \qquad\qquad NMe$$

I *Cuscohygrine* (Liebermann)　　II *Cuscohygrine* (Hess and Fink)
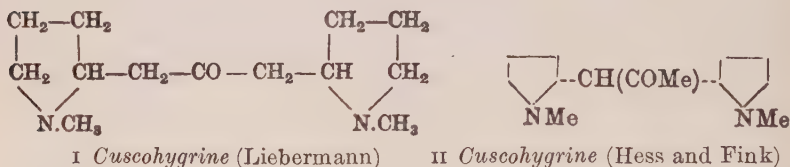
condensation products with benzaldehyde, ethyl oxalate, etc., whilst cuscohygrine does not. The behaviour of the alkaloid with nitric oxide in presence of sodium ethoxide, and the fact that it forms two isomeric hydrazones, are also in favour of the second formula.

PHARMACOLOGICAL ACTION IN THE TROPANE SERIES

More effort has probably been expended in attempts to correlate pharmacological action with chemical constitution in this series than in any other group of alkaloids. The investigations have followed three main lines, observations of changes in pharmacological action induced by (1) alterations in the aminoalcohol nucleus, (2) variation in the nature of the alkyl and acyl side chains, and (3) stereoisomerism. Before considering the results of this work, it will be convenient to summarise the characteristic actions of the principal alkaloids of the series.

Atropine. This alkaloid exhibits a complex physiological action when administered internally in toxic doses. It at first stimulates and eventually depresses the central nervous system, giving rise to hallucinations, a feeling of exaltation, inconsequent speech, delirium and convulsions, followed by stupor and coma. It paralyses the peripheral nerve endings, and in this way affects the secretory glands, the heart, and organs containing unstriped muscle. Most of the secretions are decreased owing to paralysis of the nerve ends. It is to this feature of its action that the dryness of the throat and mouth characteristic of belladonna poisoning is due. The kidney is but little affected, and consequently there is little or no change in the secretion of urine. Atropine paralyses the inhibitory terminations of the vagus in the heart. The heart is sometimes slowed and

[1] *Berichte*, 1920, **53**, 781 ; 1921, **54**, 2310.

weakened at first, but is generally quickened as a result of paralysis of the inhibitory fibres. Respiration becomes quicker and deeper, but eventually slower and shallower, and respiratory failure is the cause of death from large doses. There is often a marked rise in temperature. Atropine affects all organs containing unstriped muscle, lessening their movements, and consequently is antagonistic in this respect to muscarine and nicotine.

The alkaloid is principally used in medicine owing to its property of causing dilatation of the pupil of the eye (mydriasis). The dilatation may be induced by internal administration or by application of atropine solutions to the eye. It is due to paralysis of the motor nerve terminations in the circular muscle of the iris. At the same time the accommodation is paralysed as a result of the action of the alkaloid on the nerve endings in the ciliary muscle.

Hyoscyamine. The natural alkaloid *l*-hyoscyamine and its *d*-isomeride resemble atropine (*dl*-hyoscyamine) qualitatively in action, but the former acts much more strongly on the peripheral nerve endings than atropine.

Hyoscine (Scopolamine). This substance somewhat resembles atropine in its action on the peripheral nerve terminals ; it produces mydriasis and paralysis of accommodation more quickly than atropine, but the effect is of shorter duration. Its effects on the central nervous system are quite different from those of atropine ; as a rule it induces a feeling of fatigue and drowsiness, though in many cases there is a short stage of excitement, with giddiness and indistinct speech, especially when large doses are used.

Meteloidine. This alkaloid has no marked physiological action.

Cocaine. This has a bitter taste, is mydriatic, produces local anæsthesia, and is highly toxic. After absorption, or when taken internally, it acts chiefly on the central nervous system, causing delusions, impaired vision, and paralysis of various kinds ; large doses induce convulsions, and death occurs from paralysis of the respiratory centre.[1] Cocaine is chiefly used in medicine as a local anæsthetic. At first it was employed almost entirely in minor surgical operations, but in recent years its use has been largely extended.

Tropacocaine. This is the only other coca alkaloid which has found direct use in medicine. It resembles cocaine generally in

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[1] For a useful summary of the action of cocaine in comparison with that of other local anæsthetics, *see* Dale and others, *Lancet*, March 22, 1924, p. 596.

action, but produces local anæsthesia more rapidly, is less poisonous, and causes little or no mydriasis.

Effect of Changes in Structure on Pharmacological Action. Of the five active alkaloids referred to above, two, atropine and its *l*-isomeride, hyoscyamine, are markedly mydriatic ; two, cocaine and tropacocaine, possess in a very high degree the property of producing local anæsthesia; whilst the fifth, hyoscine, though it exhibits both these properties, is distinguished by and is now used mainly for, its sedative effects.

Tropine itself is not mydriatic, though it is stated to produce mydriasis in cats when injected in large doses. Probably the simplest mydriatic substance so far known is dimethylaminopropyl alcohol,[1] and the existence of this and of other substances, *e.g.*, ephedrine (p. 345) capable of producing mydriasis, makes it clear that this is not an effect peculiar to derivatives of tropane. Whilst tropyltropëine (atropine) is mydriatic, both benzoyltropëine and benzoyl-ψ-tropëine lack this property, though both produce local anæsthesia, and this parallelism in the influence of the tropyl and benzoyl radicals in developing mydriatic action and local anæsthetic action respectively, has been shown by von Braun and his co-workers to occur through an extensive series of hydroxyalkylamines in addition to tropine. Considerable modification may be made in the structure of tropine without impairing its capacity for yielding mydriatics and local anæsthetics. Thus atropine methobromide and methonitrate [2] have been introduced as substitutes for atropine, and von Braun and his colleagues [3] have shown that the tropyl- and benzoyl-esters respectively of homotropine (I) and of *N*-hydroxyalkylnortropanes (III) are comparable with atropine and tropacocaine (derived from tropine (II) and ψ-tropine (II)), respectively as mydriatics and local anæsthetics.

$$
\begin{array}{ccc}
\text{CH}_2\cdot\text{CH}\text{---}\text{CH}\cdot\text{CH}_2\cdot\text{OH} & & \\
| \quad \text{NMe} \quad | \quad \text{CH}_2 & & \\
\text{CH}_2\cdot\text{CH}\text{---}\text{CH}_2 & & \\
\text{I} & &
\end{array}
$$

$$
\begin{array}{c}
\text{CH}_2\text{---}\text{CH}\text{------}\text{CH}_2 \\
| \qquad\qquad | \\
\text{N.CH}_3 \quad \text{CHOH} \\
| \qquad\qquad | \\
\text{CH}_2\text{---}\text{CH}\text{------}\text{CH}_2 \\
\text{II}
\end{array}
$$

$$
\begin{array}{c}
\text{CH}_2\text{---}\text{CH}\text{----------}\text{CH}_2 \\
| \qquad\qquad\qquad | \\
\text{N(CH}_2)n\text{OH} \quad \text{CH}_2 \\
| \qquad\qquad\qquad | \\
\text{CH}_2\text{---}\text{CH}\text{--------}\text{CH}_2 \\
\text{III}
\end{array}
$$
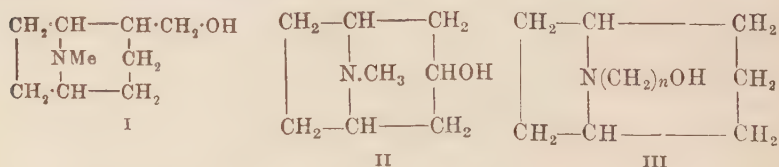
The most interesting point about the *N*-hydroxyalkylnortro-

[1] Wichura, *Zeit. Exper. Path. und Ther.* 1919, **20**, 1.

[2] Aronheim, *Berl. klin. Woch.* 1904, p. 756 ; also German Patent 228,204 and Issekutz, *Zeit. Exper. Path. und Ther.* 1917, **19**, 99.

[3] *Berichte*, 1918, **51**, 235 ; 1920, **53**, 601 ; German Patents 296,742, 299,806, 301,870 (*Chem. Soc. Abstr.* 1918 [i], 235).

panes (III), is that anæsthetic action is at its maximum when the hydroxyl group (in the chain of n-carbon atoms attached to the nitrogen atom) is in the γ-position, whilst the β-position is the most favoured for the development of mydriatic action, the acyl group being benzoyl- and tropyl- respectively.   This relationship holds throughout a series of other hydroxyalkylamines prepared by the same workers [1] from aliphatic amines, piperidine, pyrrolidine, coniine, *iso*quinoline and *iso*indole.   For example, in the substances represented by the following formulæ, IV is more active as a mydriatic than V, and V more potent as a local anæsthetic than IV, when the tropyl group (Tr) is replaced by benzoyl (Bz).

$$CH_2.CH_2.CH_2$$
$$|$$
$$CH_2.CH_2.N.CH_2.CH_2.OTr$$
$$IV$$

$$CH_2.CH_2.CH_2$$
$$|$$
$$CH_2.CH_2.N.CH_2.CH_2.CH_2.OTr$$
$$V$$

$$CH_2.CH_2.CHPr$$
$$|$$
$$CH_2.CH_2.N.CH_2.CH_2.OBz$$
$$VI$$

$$CH_2—CH———CH_2$$
$$|\quad N(CH_2)_2OH \quad CH$$
$$CH_2—CH———CH$$
$$VII$$

$$CH_2—CH—CH_2$$
$$|\quad\quad|\quad\quad|$$
$$CH_2 \quad NMe \quad CO$$
$$|\quad\quad|\quad\quad|$$
$$CH_2—CH—CH_2$$
$$VIII$$

$$CH_2—CH—CH_2$$
$$|\quad\quad|\quad\quad|$$
$$CH_2 \quad NMe \quad CH.OH$$
$$|\quad\quad|\quad\quad|$$
$$CH_2—CH—CH_2$$
$$IX$$
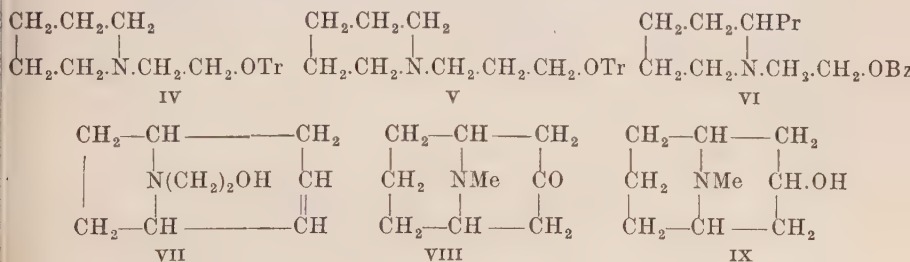
Further, in these latter cases, substitution in the α- position with respect to N in the heterocyclic ring, has at the best only a slight effect, in enhancing either action, whence the conclusion is drawn that the bicyclic system of tropane is not specific in its influence on pharmacological action, and the second ring may be regarded as making up the ballast of the whole molecule.

Thus the derivative of coniine (VI) corresponding to IV, is scarcely more active than IV (Bz replacing Tr) as a local anæsthetic. The parallelism is, however, not complete, thus the dehydrogenation of N-β-hydroxyethylnortropane, giving the corresponding nortropidine [2] (VII), enhances the local anæsthetic action of the benzoyl derivative, but reduces the mydriatic effect produced by the tropyl ester.

Not only may tropane be extended externally as in homotropine, but a new methylene group may be inserted in the heptamethylene ring : thus Werner has shown that ψ-pelletierine (VIII) on reduction in different ways yields two granatylamines (IX), corresponding, no

[1] *Berichte*, 1922, **55**, 1666.   *Cf.* Launoy and Fujimori, *Compt. rend. Soc. Biol.* 1919, **82**, 732 ; and German Patent 382,137 (1924).

[2] For a similar series of anhydronorecgonine derivatives, *see* German Patent 301,139 (*Chem. Soc. Abstr.* 1918 [i], 121).   *Cf.* von Braun and Müller, *Berichte*, 1918, **51**, 235.

doubt, to tropine and ψ-tropine, one of which on esterification with tropic or mandelic acid yields mydriatics comparable with atropine in activity.[1] And in like manner Tanret has found that these aminoalcohols on esterification with benzoic acid and certain of its derivatives yield local anæsthetics, whilst McElvain and Adams have synthesised a ring homologue of ecgonine and esterified this with ethyl alcohol and benzoic acid, and so produced a substance which is less anæsthetic and more toxic than cocaine.[2] Though the capacity for producing mydriatic substances appears to reside in the hydroxyalkylamine nucleus, its development depends largely on the nature of the acid used in esterifying it. This subject has been investigated very thoroughly by Jowett and Pyman, and on the pharmacological side by Marshall, Dale, Laidlaw and Cushny. Jowett and Pyman[3] observed the effect of comparable solutions of the various tropëines by instillation into the conjunctival sacs of cats, and drew the following conclusions as to the influence of the acyl group :

I. Tropëines of aliphatic acids exert no mydriatic effect.

II. The replacement of the benzene residue by that of pyridine in the acyl group of a mydriatic tropëine, does not cause the activity to vanish.

III. In tropëines containing a disubstituted benzene ring, those in which the replacing groups occupy the *para* position have the least mydriatic action ; thus *o*- and *m*-hydroxybenzoyltropëines are active, but not the *p*-isomeride.

IV. No generalisation as to the relation between the mydriatic action and chemical constitution of the tropëines can be made at present, which will explain the observed facts.

More recently Cushny[4] has compared the action of *d*- and *l*-hyoscyamines with that of atropine, and of *d*-homatropine with that of *dl*-homatropine in antagonising the action of pilocarpine, and finds that the order of activity of the first three is in the ratio 1 : 40 : 20, and of the second two in the ratio 4 : 2·5. Cushny draws attention

[1] *Journ. Amer. Chem. Soc.* 1918, **40,** 669.   *Cf.* Tanret, *Compt. rend.* 1923, **176,** 1659.

[2] McElvain and Adams, *Journ. Amer. Chem. Soc.,* 1923, **45,** 2738.

[3] *Proc. 7th Int. Cong. Appl. Chem.* London, 1909.   *Cf.* Pyman, *Trans. Chem. Soc.* 1917, **91,** 1104.   See also *Trans. Chem. Soc.* 1906, **89,** 357 ; 1907, **91,** 92 ; 1909, **95,** 1020.

[4] *Journ. Pharm. Exp. Ther.* 1920, **15,** 105.   *Cf. Journ. Physiol.* 1904, **30,** 176.   The first paper also contains a useful bibliography of previous work.

especially to the important influence of the acyl radical in the
tropëines, which exercises the maximum effect when it is a hydroxy-
aromatic residue and is lævorotatory, and gives the following
table of relative activities, in illustration of this point :

l-Hyoscyamine .	. . 600	*dl*-Homatropine . . 10
d-Hyoscyamine	. . 15	Phenylacetyltropine . . 7
dl-Hyoscyamine	. . 300	Benzoyltropine . . 1
Methylatropine	. . 450	*o*-Hydroxybenzoyltropine . 1
d-Tartryltropine	. . 0	*m*-Hydroxybenzoyltropine . $<$1
l-Homatropine	. . 14	*p*-Hydroxybenzoyltropine . $<\frac{1}{2}$
d-Homatropine	. . 7	

The same author finds that *l*-hyoscine is sixteen to eighteen times
as active as the *d*-isomeride in antagonising the action of pilocarpine [1]
on the termination of nerves in the salivary glands, whilst both
isomerides are equally active on nerve ends in striated and un-
striated muscle, and on the central nervous system.   It is interesting
in this connection to note that the tropyl and mandelyl-esters of
ψ-tropine (stereoisomerides, cis-trans type, of atropine and homatro-
pine respectively) are stated to exert no mydriatic effect, whilst
d-ψ-cocaine, on the contrary, is said to have much the same anæs-
thetic action as *l*-cocaine.[2]   The influence of the nature of the acyl
group in the production of local anæsthetics has also been discussed
by Jowett and Pyman,[3] who point out that this property is shown
by alkamine esters of widely different structure, but possessing the
following characters :

(1) The acyl group may be benzoyl or a substituted aromatic
    residue.

(2) The amino group may be secondary or tertiary or be asso-
    ciated with simple or bridged ring complexes.

(3) The alcohol group may be primary, secondary, or tertiary,
    and may separate the acyl and amino groups by a chain of
    two or three carbon atoms.

Illustrations of this wide variation in structure associated with
capacity to produce local anæsthesia, may be found among the
numerous synthetic alkamine esters that have been introduced and

[1] *Journ. Pharm. Exp. Ther.* 1921, **17,** 41.   *Cf. Journ. Physiol.* 1905,
32, 501 ; *Arch. Exp. Path. Pharm.* 1912, **70,** 433 ; and Hug *ibid.* 1912,
69, 45.

[2] Liebrich, *Berichte*, 1892, **25,** 933, compare, however, Gottlieb,
Arch. Exp. Path. Pharm. 1923, **97,** 113, who states that it is more active.

[3] *Proc. 7th Int. Congr. Appl. Chem.* London, 1909.   *Cf.* Pyman, *Trans.
Chem. Soc.* 1917, **91,** 1104.

used as cocaine substitutes, *e.g.*, stovaine (I), alypine (II), and benzamine (III) :

$$CH_3 \quad O.CO.C_6H_5$$
$$>C<$$
$$C_2H_5 \quad CH_2.NMe_2.HCl$$

I

$$NMe_2.CH_2 \quad O.CO.C_6H_5$$
$$>C<$$
$$C_2H_5 \quad CH_2.NMe_2.HCl$$

II

$$CH.O.CO.C_6H_5$$
$$CH_2 \qquad CH_2$$
$$Me.CH \qquad CMe_2$$
$$NH.HCl$$

III
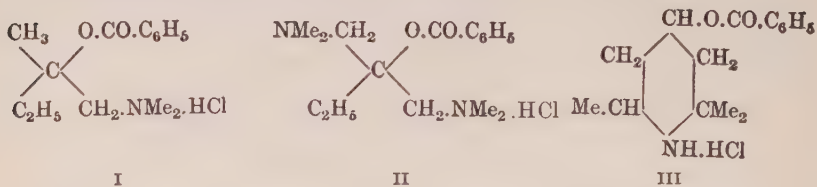
The property of producing local anæsthesia is also shown by other products than alkamine esters, *e.g.*, benzyl alcohol and its homologues, saligenin, and the esters of aminoaromatic acids, and several of these are now manufactured for this purpose, *e.g.*, ethyl 4-aminobenzoate and diethylaminoethyl 4-aminobenzoate.

Several of these cocaine substitutes contain asymmetric carbon atoms, but very little attention has yet been given to the study of the influence of optical activity on their local anæsthetic action. King has shown [1] that in the case of β-eucaine (benzamine : formula (III), above) there is no difference in the anæsthetic action of the *d*- and *l*-forms, but that the *l*-form is twice as toxic as the *d*-form. In the case of cocaine, on the contrary, Gottlieb [2] found that *dl*-ψ-cocaine was a more powerful anæsthetic than *dl*-cocaine, that the *d*-forms both in the ordinary and ψ-cocaines were more active than the *l*-forms, and also that the ψ-cocaines were less toxic than the ordinary cocaines, and in both series the *d*-isomerides less toxic than the *l*-isomerides.

[1] *Trans. Chem. Soc.* 1924, **125**, 46.
[2] *Arch. Exp. Path. Pharm.* 1923, **27**, 113 ; *Zeit. Physiol. Chem.* 1923, **130**, 374.

ALKALOID OF *DIOSCOREA HIRSUTA*

Dioscorine, $C_{13}H_{19}O_2N$, was obtained from the tubers of *Dioscorea hirsuta*, Blume, by Boorsma,[1] and was afterwards investigated by Schutte [2] and by Gorter.[3] It forms greenish-yellow plates, m.p. 43·5°, distils unchanged *in vacuo*, is soluble in water, alcohol, or chloroform, and sparingly so in ether or benzene. The hydrochloride, $B.HCl.2H_2O$, forms colourless needles, m.p. 204°, $[\alpha]_D + 4° 40'$, from alcohol ; the platinichloride, $(B.HCl)_2PtCl_4.3H_2O$, orange-yellow tablets, m.p. 199°–200° (*dry*) ; the aurichloride, $B.HAuCl_4$, yellow needles, m.p. 171° (*dry*).

With sulphuric acid and potassium iodate, dioscorine gives a blue-violet coloration, and a reddish-violet with sodium nitroprusside in presence of alkalis.

According to Gorter, dioscorine decolorises permanganate immediately, contains a : NCH_3 but no —OH or —OMe group. When heated with potash it yields a salt from which acids regenerate the alkaloid, so that the latter is probably a γ-lactone. By exhaustive methylation, dioscorine gives first demethyl-dioscoridine, $C_{13}H_{21}N$, and eventually trimethylamine and a hydrocarbon, $C_{11}H_{14}$, which appears to be a butenyl*cyclo*heptatriene,

$\overline{CMe_2 : CH.C : CH.CH : CH.CH_2.CH : CH}$. On these and other grounds Gorter [4] assigns the annexed formula to the alkaloid :

$$
\begin{array}{c}
CH_2-CH-CH_2 \\
|\quad\quad |\quad\quad | \\
|\quad\quad NMe\;\; CH.O.CO \\
|\quad\quad |\quad\quad |\quad\quad | \\
CH_2-CH-CH-\!-C : CMe_2
\end{array}
$$
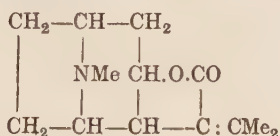
Dioscorine is bitter and poisonous ; it produces paralysis of the central nervous system, and, in general, behaves like picrotoxin. This action appears to be correlated with the —CO.C : C— group, since on the suppression of this, as in the corresponding acid, or the reduced product, bisdihydrodioscorine $(C_{13}H_{20}O_2N)_2$, the picrotoxin-like action disappears.

[1] *Meded. uit's Lands Plantentuin*, 1894, p. 13.
[2] *Chem. Centr.* 1897 [ii], 130.
[3] *Ann. Jard. Bot. Buit.* 1909 [ii], *Suppl.* **3,** 385.
[4] *Rec. Trav. Chim.* 1911, **30,** 161.

ALKALOIDS OF *CYTISUS SCOPARIUS*

Quinuclidine Sub-group.

Under the name " broom tops " the herbaceous branches of the common broom, *Cytisus scoparius* (*Sarothamnus scoparius*), were at one time used to a considerable extent in medicine. From this material Stenhouse [1] isolated the alkaloid sparteine, with which " lupinidine " obtained from yellow lupin seeds is identical. [2] According to Chevalier, broom tops yield 0·23 to 0·68 per cent. of sparteine, depending on the season of collection, being richest in March and poorest in August after flowering. [3] In 1918, Valeur [4] isolated two new alkaloids from this source, viz., SAROTHAMNINE and GENISTEINE. The former occurs in the mother liquors left in the manufacture of sparteine sulphate, and forms crystalline addition products with certain solvents, *e.g.*, $C_{15}H_{24}N_2.\frac{1}{2}CHCl_3$, m.p. 127°, $[\alpha]_D - 38\cdot7°$ and $C_{15}H_{24}N_2.\frac{1}{2}EtOH$, m.p. 99°, $[\alpha]_D - 25\cdot6°$. It is an unsaturated base and reduces permanganate. *Genisteine*, $C_{16}H_{28}N_2$, is a volatile alkaloid, m.p. 60·5°, b.p. 139·5° to 140·5°/5 mm., obtained by rendering the ultimate mother liquors from sparteine and sarothamnine alkaline and extracting with ether. It yields a hydrate, $B.H_2O$, m.p. 117°, $[\alpha]_D - 52\cdot3°$ in alcohol, a picrate, $B.2C_6H_2(NO_2)_3.OH$, m.p. 215°, and a platinichloride, $B.H_2PtCl_6.2\frac{1}{2}H_2O$.

Sparteine, $C_{15}H_{26}N_2$. The alkaloid is prepared by extracting ground broom tops with dilute sulphuric acid, concentrating the extract, adding excess of alkali, and distilling the liberated alkaloid in a current of steam. The distillate is exactly neutralised with hydrochloric acid, evaporated to dryness, and the residue distilled over solid potash. The distillate is finally purified by redistillation in a current of hydrogen, metallic sodium being used to remove the last traces of water.

Sparteine is a colourless oil, D^0 1·034, D^{20} 1·0196, $[\alpha]_D^{21} - 16\cdot42°$ in alcohol, b.p. 188° under 18 mm. pressure, or 325° in hydrogen under 754 mm. pressure. It has a bitter taste, an odour recalling that of aniline, and is sparingly soluble in water (1 in 328 at 22°), [5] but readily so in alcohol, chloroform or ether. The base is strongly alkaline, and is monoacidic to litmus or phenolphthalein, but

[1] *Journ. Chem. Soc.* 1852, **4**, 216.
[2] Willstätter and Marx, *Berichte*, 1904, **37**, 2351.
[3] *Compt. rend.* 1910, **150**, 1069.
[4] *Ibid.* 1918, **167**, 26, 163.
[5] *Cf.* Valeur, *ibid.* 1917, **164**, 818 ; and *Bull. Sci. pharmacol.* 1919, **26**, 145.

diacidic to methyl orange. It forms well-crystallised salts and behaves as a diacidic base. The sulphate, $B.H_2SO_4.5H_2O$, m.p. 136° (*dry*), $[\alpha]_D^{15} - 22 \cdot 12°$ in water, forms transparent, columnar crystals soluble in 1·1 of water at 25°, or 2·4 of alcohol at 25°, $[\alpha]_D - 22°$. This salt is used in medicine. The dihydriodide, $B.2HI$, has m.p. 257°–258° (225°, *dry*, Corriez). The platinichloride, $B.H_2PtCl_6.2H_2O$, m.p. 243·5° (*decomp.*), forms rhombic prisms from dilute hydrochloric acid ; the aurichloride has m.p. 193·4° on immediate precipitation, but after recrystallisation melts at 183·4°, and then has a composition represented by the formula, $B_2.4HCl.3AuCl_3$ (E. Schmidt). The picrate, m.p. 208°, forms glancing yellow needles from boiling alcohol.

Reactions and Constitution. According to Jorissen [1] sparteine is distinguished from other alkaloids by giving a bulky red precipitate when hydrogen sulphide is passed through sulphur suspended in a solution of the base in ether. Coniine gives an orange and atropine a yellow precipitate under these conditions.

Moureu and Valeur [2] pointed out that both the nitrogen atoms in sparteine are basic and tertiary, that neither has a methyl group attached to it, and that, since the alkaloid is unaffected by reducing agents or by permanganate, it probably contains at least two saturated closed chains. Wackernagel and Wolffenstein [3] similarly suggested that sparteine was a bicyclic base containing a pyridine and a pyrrolidine ring.

Further insight into the constitution of sparteine is due chiefly to Moureu and Valeur, and has been obtained mainly by a study of its degradation by exhaustive methylation. When treated with methyl iodide in methyl alcohol, it yields two stereoisomeric mono-methiodides,[4] the α-methiodide, having a lower solubility in water and a lower specific rotation than the α'-isomeride. The former on treatment with silver hydroxide gives sparteinemethylammonium hydroxide, which, on heating, yields methylsparteine, $N:C_{15}H_{25}NCH_3$, and this, on repetition of the treatment, furnishes in turn dimethyl-sparteine and sparteinetrimethylammonium hydroxide. The latter, on heating, breaks down into trimethylamine and hemisparteilene, $C_{15}H_{23}N$. Moureu and Valeur account for these reactions by the

[1] *J. Pharm. Chim.* 1911 [vii], **4**, 251.

[2] *Compt. rend.* 1903, **137**, 194.

[3] *Berichte*, 1904, **37**, 3238. *Cf.* Willstätter and Marx, *ibid.* 1904, **37**, 2351.

[4] *Compt. rend.* 1905, **140**, 1601, 1645.

following formula for sparteine, which represents it as two quinu-clidine (p. 160) residues joined by a —CH_2— group : [1]

Sparteine   *Methylhemisparteilene*
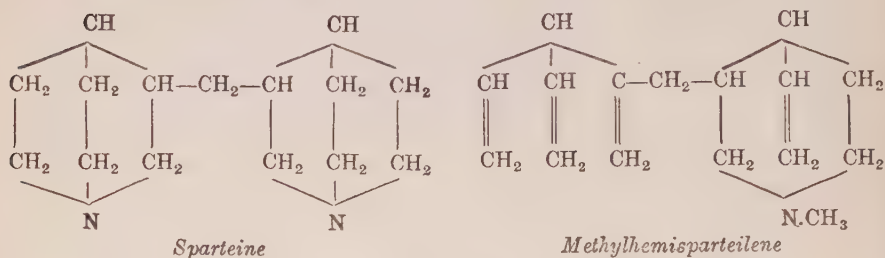
Dimethylsparteine gives a dimethiodide which, with moist silver hydroxide, yields tetramethylsparteineammonium hydroxide, $C_{15}H_{24}Me_2N_2(MeOH)_2$, and this on distillation furnishes trimethyl-amine and methylhemisparteilene, $C_{16}H_{25}N$, which contains an : NCH_3 group and four ethylenic linkages, and from its mode of formation must have the structure shown above, if Moureu and Valeur's formula for sparteine is accepted.   By exhaustive methyla-tion of methylhemisparteilene the hydrocarbon sparteilene, $C_{15}H_{20}$, is obtained, the same series of changes now taking place in the second ring.[2]

Moureu and Valeur have also shown that in the action of silver hydroxide on sparteine α-methiodide two methylsparteines, distin-guished as α- and β-, are produced, and that the dihydriodide of the former, when heated with water at 125°, is partly converted into the methiodide of a new saturated ditertiary base,[3] *iso*sparteine (b.p. 177·5° under 16·5 mm., $[\alpha]_D - 25·01°$ in alcohol).   These changes are assumed to take place as shown in formulæ on top of next page, that is, the formation of *iso*sparteine involves the opening of the piperidine ring (a in formula 1) by the rupture of the bridge, and its subsequent reclosing to form a pyrrolidine ring (a' in formula 3).   The reverse change occurs when *iso*sparteine-methosulphate is heated with baryta, this substance passing into the corresponding methohydroxide, which at 100° *in vacuo* is con-verted into α-methylsparteine.[4]

Oxidation experiments with sparteine have not, so far, led to very

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[1] *Compt. rend.* 1905, **141,** 117, 261, 328 ; 1907, **145,** 815. *Cf.*, however, 1912, **154,** 309 ; and Germain, *Gazzetta,* 1912, **42,** i, 447.

[2] *Compt. rend.* 1912, **154,** 161.

[3] *Ibid.* 1907, **145,** 929, 1184, 1343 ; 1908, **146,** 79 ; 1911, **152,** 386, 527.

[4] Valeur, *ibid.* 1908, **147,** 127, 864, 1318.

$$C_8H_{14}N$$
$$|$$
$$CH\!-\!CH_2$$

$$CH\!-\!CH_2\!-\!CH_2\!-\!N(CH_3).OH \;\longrightarrow$$
$$(a)$$
$$CH_2\!-\!CH_2$$
$$(1)$$

a-Methylsparteinum hydroxide

$$C_8H_{14}N$$
$$|$$
$$CH\!-\!CH_2$$

$$CH\!-\!CH=CH_2 \qquad NCH_3 \;\longrightarrow$$

$$CH_2.CH_2$$
$$(2)$$

a-Methylsparteine

$$C_8H_{14}N$$
$$|$$
$$C:CH_2$$

$$CH\!-\!CH_2\!-\!CH_2\!-\!NCH_3$$

$$CH_2\!-\!CH_2$$
$$(4)$$

β-Methylsparteine

$$C_8H_{14}N$$
$$|$$
$$CH.\;CH_2$$

$$CH\!-\!CHMe\!\!-\!\!-\!\!-\!N$$
$$(a')$$
$$CH_2.CH_2$$
$$(3)$$
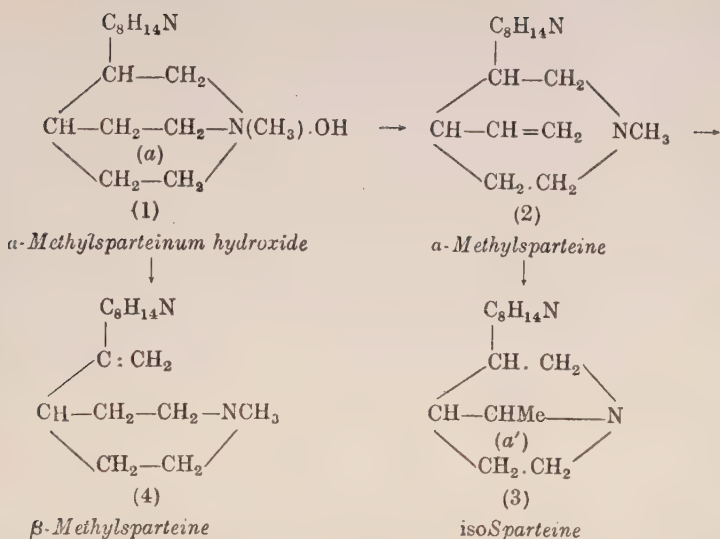
isoSparteine

useful results. Willstätter and Marx,[1] by oxidising sparteine sulphate with chromic acid, obtained SPARTYRINE, $C_{15}H_{24}N_2$, together with OXYSPARTEINE, $C_{15}H_{24}ON_2$, already obtained by Ahrens, and a third base, $C_{15}H_{24}O_4N_2$. Spartyrine, m.p. 153°–154°, $[\alpha]_D^{18\cdot5} - 25\cdot96°$ is crystalline, yields a crystalline hydrochloride and platinichloride, and contains an ethylenic linkage ; it appears to be formed by such a change as the following in a portion of the sparteine molecule :

$$\cdot C \!\!\diagup\!\!\diagdown\! CH.CH \!\!\diagup\!\!\diagdown \;\longrightarrow\; \cdot C\!\!\diagup\!\!\diagdown\! C(OH).CH\!\!\diagup\!\!\diagdown \;\longrightarrow\; \cdot C\!\!\diagup\!\!\diagdown\! C:C\!\!\diagup\!\!\diagdown$$
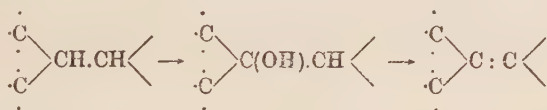
Oxysparteine, m.p. 87·5°, b.p. 209° under 12·5 mm., $[\alpha]_D^{18} - 10\cdot04°$ is regarded as formed by an extension of the same process thus :

$$\cdot C\!\!\diagup\!\!\diagdown\! CH.CH\!\!\diagup\!\!\diagdown \;\longrightarrow\; \cdot C\!\!\diagup\!\!\diagdown\! C(OH).C(OH)\!\!\diagup\!\!\diagdown \;\longrightarrow\; \cdot C\!\!\diagup\!\!\diagdown\! C.O.C\!\!\diagup\!\!\diagdown$$
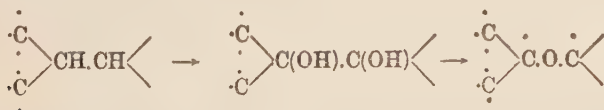
More recently Valeur and Luce have investigated the action of hydrogen peroxide on sparteine and *iso*sparteine,[2] and on the rather slender evidence that succinic acid is produced by the action of

[1] *Berichte*, 1905, **38**, 1772.
[2] *Compt. rend.* 1919, **168**, 1276.

permanganate on sparteine in presence of phosphoric acid, Germain [1] has modified Moureu and Valeur's formula by connecting the two bicyclic nuclei by a $—CH_2.CH_2—$ chain, and reducing the bridge in one of the bicyclic rings to one carbon atom.

Physiological Action.—Sparteine closely resembles coniine in its physiological action. It appears to exert little effect on the central nervous system, but paralyses the motor nerve terminations and the sympathetic ganglia. It also causes greater depression of the heart's action than coniine, and is less active in increasing arterial tension when injected into a vein. It is poisonous, but less so than coniine. Broom tops were used in medicine chiefly as a diuretic, this action being due, not to the sparteine they contain, but to a neutral substance, scoparin, also present in the plant.

ALKALOID OF *RETAMA SPHÆROCARPA*

This plant, allied to broom and also to laburnum (p. 394), may appropriately be dealt with here. It contains the alkaloid RETAMINE, $C_{15}H_{26}ON_2$, crystallising in colourless needles, m.p. $162°$, $[\alpha]_D +43·15°$ in alcohol. This is a strongly alkaline, diacidic base, yielding crystalline salts and giving the colour reactions of sparteine of which it may be a hydroxy-derivative. It is bitter, but physio·logically inactive.[2]

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[1] *Gazzetta*, 1912, **42** [i], 447; *Chem. Soc. Abstr.* 1912 [i], 579; Valeur, *Compt. rend.* 1908, **147**, 127, 864.

[2] Battandier and Malosse, *Compt. rend.* 1897, **125,** 360, 450.

IV. QUINOLINE GROUP

ALKALOIDS OF *CINCHONA* SPECIES

(*Quinolylquinuclidine Sub-group*)

THIS group of natural alkaloids occurs in the various species of the two Rubiaceous genera, *Cinchona* and *Remijia*, indigenous to the eastern slopes of the Andes between the latitudes 10° N. and 20° S. Cinchona is found on an average from 5,000 to 8,000 feet above sea-level, the highest limit being 11,000 and the lowest 2,500 feet. It is uncertain whether the antipyretic properties of the barks of these plants were known to the natives before the advent of the Spaniards; it was generally believed at the commencement of the eighteenth century that this was the case, as is shown by Arrot,[1] who travelled in South America in 1737; but Humboldt was informed at Loxa in 1807 that the natives regarded cinchona bark as a dangerous drug, and that the cascarilleros, who collected it for export, were convinced that the only purpose for which it could be employed was the dyeing of cloth. Similar statements were made by Pöppig in 1830 and by Spruce in 1860, whilst Markham, in 1862, observed that the native doctors never used cinchona bark. The bark was first employed in Europe in 1639, and its introduction is described by Chifflet in a pamphlet published at Brussels in 1653; two years later it was sold in England under the name " Jesuits' powder," and was prescribed by Brady at Cambridge about 1658, and by Willis in London about 1660. It first appears in the London Pharmacopœia published in 1677 under the name *Cortex Peruanus*. Summaries of the history of cinchona will be found in Flückiger and Hanbury's *Pharmacographia*,[2] and in a paper by Mr. D. Howard.[3]

The genus *Cinchona* was established by Linnæus in 1742, and the tree now known as *Cinchona officinalis* was described by him in 1753. Soon after the introduction of the drug into Europe, the demand for it became so great that there was some prospect of a total extinction

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[1] *Phil. Trans.* 1737, **40**, 81.

[2] Macmillan & Co., London, 1874.

[3] *Journ. Soc. Chem. Ind.* 1906, **25**, 97.

of the plants in South America, and attention was directed to the possibility of cultivating the trees in other countries. This was attempted about 1860 in India, Ceylon, Jamaica, Australia and Java, but was only thoroughly successful from the first in India and Ceylon. Of late years the cultivation has declined in these countries and has enormously increased in Java, so much so that the latter is now the most important cinchona district in the world,[1] a position which is chiefly the result of the long-continued chemical and botanical investigations carried out under the auspices of the Dutch East Indian Government.

In order to secure a continuous supply of bark without destroying the trees, new methods have been introduced from time to time, such as stripping off portions and covering the wounds with moss, whereby a formation of " renewed bark " is produced, which generally contains a larger proportion of alkaloids than that due to natural growth. In Java it was found that the outer bark could be shaved off in small pieces periodically without inflicting injury on the tree. In recent years these methods of harvesting have been supplemented by " coppicing "—bark being stripped from the cut branches. The first attempts at cinchona cultivation, both in India and Java, were made with *Cinchona succirubra*, the hardiest of the known species, and this advantage was considered to outweigh the smallness of its yield in quinine. Subsequently a variety of *Cinchona Calisaya* was discovered by Ledger, the bark of which gave a higher yield of quinine than any of the known cinchonas, but the plant being more difficult to rear than *C. succirubra*, did not find favour with Indian planters. In Java it is raised by grafting seedlings upon a young stock of the hardier *succirubra*, the latter being largely cut away when the graft becomes well established. Young trees grown in this way are planted rather thickly, and after three years are coppiced, this process being continued yearly until the increasing girth of the stems renders necessary the removal of a certain number of the trees, which are uprooted, and the whole of the bark from root and stem collected. The remainder are dealt with as already described until the trees become mature, when they are all uprooted, stripped of bark, and a fresh plantation formed.

In recent years attention has been more and more devoted to the selection of cinchona hybrids for cultivation, on the basis of the

[1] For a detailed account of the world's trade in cinchona bark see " Indian Trade Enquiry Reports on Drugs and Tanning Materials," London, John Murray, 1922.

richness of the bark in quinine, and to the production of varieties which will combine this quality with resistance to disease and large yield.

The alkaloids of practical importance belonging to this group are quinine, quinidine, cinchonine and cinchonidine, but, in addition to these, over twenty alkaloids have been isolated from various species of cinchona and cuprea. Their names and formulæ are as follows :

Formula			Name
$C_{16}H_{18}ON_2$	.	.	Paricine.
$C_{19}H_{22}ON_2$	.	.	Cinchonine, cinchonicine, cinchonidine, homocinchonidine.
$C_{19}H_{24}ON_2$	.	.	Cinchotine, cinchamidine, cinchonamine.
$C_{19}H_{22}O_2N_2$	.	.	Cupreine.
$C_{19}H_{24}O_2N_2$	.	.	Quinamine, conquinamine.
$C_{20}H_{24}O_2N_2$	.	.	Quinine, quinidine, quinicine.
$C_{20}H_{26}O_2N_2$	.	.	Hydroquinine, hydroquinidine.
$C_{22}H_{26}O_4N_2$	.	.	Chairamine, conchairamine, chairamidine, conchairamidine.
$C_{23}H_{26}O_4N_2$	.	.	Cusconine, concusconine, aricine.
$C_{38}H_{44}O_2N_4$	.	.	Dicinchonine.
$C_{40}H_{46}O_4N_4$	.	.	Diconquinine.
Composition unknown			Javanine, cuscamine, cuscamidine, cusconidine.

Estimation of Alkaloids in Cinchona Barks.

The analysis of cinchona barks and the estimation of the more important alkaloids are subjects with a literature of their own, far too extensive to be even briefly surveyed here, and the methods given below are included merely to indicate the principles on which these analyses are made. For a full account of these subjects the reader should consult Allen's " Organic Analysis," [1] 4th edition, Vol. VI., pp. 479–550. Methods for the approximate estimation of the more important alkaloids separately, usually depend on the different solubilities of the periodides, sulphates, tartrates or hydriodides.

British Pharmacopœia, 1914. The dried bark of *Cinchona succirubra* is the only cinchona bark official in this pharmacopœia, and the following process for its assay is prescribed : Ten grammes of the bark in No. 60 powder are mixed with 6 grm. of slaked lime,

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[1] London, J. & A. Churchill, 1912. New edition in the press.

and the whole moistened with 22 c.c. of water and set aside for two hours. The mass is then transferred to a flask fitted with a reflux condenser, and boiled with 130 c.c. of " benzolated amyl alcohol " (benzene 3 vols., amyl alcohol 1 vol.) during thirty minutes. The solvent is decanted through a filter into a separator, and ebullition with the same quantity of solvent repeated twice. The contents of the flask are finally turned out on the filter and washed with fresh portions of the solvent till exhausted, all the liquors being collected in the separator. The mixed warm liquors are shaken (1) with 2 c.c. of diluted hydrochloric acid (sp. gr. 1·048) mixed with 12 c.c. of water ; (2) with water acidified with dilute hydrochloric acid, fresh portions being used until alkaloid is no longer extracted. The mixed acid liquors are then exactly neutralised with dilute ammonia solution and concentrated to 16 c.c. To this 1·5 grm. of sodium potassium tartrate, dissolved in 3 grm. of water are added, the mixture stirred well and set aside one hour. The precipitated tartrates of quinine and cinchonidine are collected on a tared filter, washed with water, dried at 100°, and their weight w determined. The combined percentage of these two alkaloids in the bark is given by the formula, $w \times 0·8 \times 10$.

The mother liquor and washings are then treated with ammonia solution in slight excess, and the " other alkaloids " extracted by agitation successively with three portions of 10 c.c. of chloroform, the mixed chloroformic solution being evaporated to dryness, dried at 110° and weighed (w'). The percentage of " other alkaloids " in the bark is equal to $10w'$. The percentage of " total alkaloids " in the bark is equal to $10(0·8w + w')$. The " total alkaloids " should be between 5 and 6 per cent., of which not less than half should be quinine and cinchonidine.

United States Pharmacopœia (9th Rev.). This recognises (1) cinchona bark, which may be derived from *C. Ledgeriana, C. Calisaya,* or hybrids of these with other species of cinchona ; and (2) red cinchona bark derived from *C. succirubra*. The same assay process is prescribed for both.

Five grammes of cinchona bark in No. 40 powder are mixed in a 500 c.c. flask with 200 c.c. of a mixture of ether (2 vols.), chloroform (1 vol.), shaken well and left to stand ten minutes ; 5 c.c. of ammonia water (sp. gr. 0·958 at 25°) are then added, and the whole shaken frequently during one hour, and left to stand eight to ten hours. Ten cubic centimetres of distilled water are next added, and the flask shaken vigorously. One hundred and sixty cubic centimetres

of the liquid (4 grm. of bark) are decanted through a small plug of cottonwool into a separator and the alkaloids extracted by shaking repeatedly with dilute sulphuric acid. The combined acid liquids are rendered alkaline with ammonia water, and the alkaloids extracted completely with chloroform. The chloroform solution is evaporated on a water-bath, the residue dissolved in 5 c.c. of alcohol and redried. It is finally dried at 100°, and its weight n determined. The percentage of total alkaloids in the bark is given by the formula $25n$. It should not be less than 5.

Both pharmacopœias also prescribe processes of assay for galenical preparations of cinchona bark.

Estimation of Quinine in Cinchona Bark. From 1 to 5 grm. of total alkaloids extracted by the United States Pharmacopœia method from the bark, may be used for the estimation of the chief alkaloids. For the estimation of quinine, it should be exactly neutralised with $N/10$ sulphuric acid, and the resulting liquid diluted with water until it contains 1 part by weight of total alkaloid in 70 parts by weight of solution. The latter is heated to 90° during five minutes, then cooled to 15° and set aside at this temperature during thirty minutes, when crystals of quinine sulphate will separate if the total alkaloids contained more than 8 per cent. of quinine. The crystals are collected on a tared filter and washed with water at 15° until the filtrate weighs 90 grm. for each gramme of total alkaloids taken. The crystals are dried at 100° and weighed. The weight requires correction for the solubility of quinine sulphate in water at 15°, and for this purpose 0·000817 grm. should be added for each gramme of filtrate and washings. The sum divided by 0·855 gives the yield of crystallised quinine sulphate.

Estimation of Cinchonidine, Cinchonine and Quinidine. For the estimation of the remaining bases it is necessary to start with about 5 grm. of the total alkaloids from which the quinine should be separated by the foregoing process. To the filtrate a slight excess of soda solution is added, and the alkaloids shaken out with chloroform, which is distilled off and the residue dissolved in sufficient dilute sulphuric acid to produce exact neutrality (*Solution A*). A saturated solution of sodium potassium tartrate is then added, the mixture allowed to stand at 15° for one hour and frequently stirred ; the precipitate is collected on a tared filter, washed with as little water as possible, the filtrate and washings being collected in a graduated cylinder and measured. The *cinchonidine tartrate* is dried

at 105° and weighed, 0·00083 grm. being added to the weight for each cubic centimetre of filtrate.

The filtrate is evaporated on the water-bath to its original volume (*Solution A*), clarified by addition of a drop of acetic acid, a saturated neutral solution of potassium iodide added and the liquid frequently stirred during two hours at 15°. The precipitated *quinidine hydriodide* is collected with the same precautions as before. The weight obtained should be corrected by the addition of 0·00077 grm. for each cubic centimetre of filtrate.

The filtrate is now made just alkaline with soda solution, and the precipitate extracted with chloroform, the latter distilled off and the residue dried and weighed as cinchonine, the weight being corrected by the deduction of 0·00052 grm. for each cubic centimetre of the original liquid (*Solution A*), and 0·00066 grm. for each cubic centimetre of the filtrate from the quinidine estimation. The cinchonine residue will also contain any amorphous alkaloids present, and for the removal of these, it may be washed with dilute alcohol (sp. gr. 0·94), the insoluble matter being purified cinchonine, which should again be weighed.

The process here outlined is a modified form of de Vrij's method,[1] recommended by Allen [2] as specially suitable for East Indian barks, and he has shortened it by substituting titration for gravimetric determination of the alkaloidal salts. Thus the cinchonidine tartrate may be washed into a beaker with boiling water, a drop of phenolphthalein added, and the mixture titrated with $N/20$ soda, each cubic centimetre of which corresponds to 0·0147 grm. of cinchonidine. In the same manner the quinidine hydriodide solution may be washed into the titration vessel with dilute potassium iodide solution and the estimation carried out as before, 1 c.c. of $N/20$ soda being equivalent to 0·0162 grm. of quinidine. The results are less accurate than those obtained gravimetrically.

Quinine, $C_{20}H_{24}O_2N_2$. This, the most important of the cinchona alkaloids, was isolated in an impure condition by Fourcroy in 1792, and described by Vauquelin under the name " quina " in 1809. In the following year a Spanish physician, Dr. Gomes, obtained by the addition of caustic potash to an alcoholic extract of cinchona bark a crystalline substance which he named " *Cinchonino*." The basic properties of this material were mentioned by Houtou-Labillardière in Paris to Pelletier and Caventou, who, inspired by the then recent

[1] *Pharm. Journ.* 1871 [iii], 2,642.
[2] *Commercial Organic Analysis*, 4th ed. vol. vi. p. 495.

observations of Sertürner on the existence of " organic alkalis " in nature, undertook the investigation of " *Cinchonino*," and resolved it into two substances, which they named *quinine* and *cinchonine*.[1] The bases were characterised by Pelletier and Dumas,[2] and the composition of quinine was accurately determined by Liebig, Regnault and Strecker, the two latter assigning to it its present formula.

Preparation. The bark, ground to a fine powder, is mixed with slaked lime and enough water to form a stiff paste, which is then dried and extracted with hot petroleum. In the laboratory a mixture of chloroform and ether may be used in place of petroleum. The alkaloids extracted from the organic solvent by shaking with successive quantities of dilute sulphuric acid consist of quinine, cinchonidine, cinchonine, and a little quinidine, and such a mixture, prepared by the addition of caustic soda, usually after the removal of quinine to the acid liquid, constitutes the " cinchona febrifuge " [3] prepared in India for distribution to the natives. The liquid on neutralisation deposits crystals of crude quinine sulphate which may be purified by recrystallising the mixed sulphates from hot water by the process described on p. 129. The salt which first separates is redissolved in boiling water, decolorised with animal charcoal, and recrystallised until sufficiently free from cinchonine and cinchonidine. Hesse [4] has stated that quinine sulphate may be freed from cinchonidine sulphate by recrystallisation twice from faintly acidulated water. Pure quinine may be prepared by precipitating the commercial sulphate as the periodide (herepathite), regenerating the base from the latter by sulphuretted hydrogen and recrystallisation from alcohol,[5] and Tutin [6] has prepared pure specimens of the alkaloid by regeneration from the recrystallised *d*-camphor-sulphonate.

Properties. Quinine is precipitated as an amorphous, colourless, bulky powder when alkalis are added to a well-cooled acid solution of the alkaloid, but in presence of ammonia this gradually passes into a crystalline efflorescent hydrate, $B.3H_2O$, m.p. 57°, which loses $1H_2O$ on exposure to air at 20°, $2H_2O$ when dried over sulphuric

[1] *Ann. Chim. Phys.* 1820 [ii], **15**, 291, 1337.

[2] *Ibid.* **24**, 169.

[3] For a discussion of the composition of cinchona febrifuge, *see* Howard and Chick, *Chemist and Druggist*, July 28, 1923, p. 145.

[4] *Pharm. Journ.* 1884 [iii], **15**, 869. *Cf. ibid.* 1885 [iii], **16**, 358, 818 and 1886 [iii], **17**, 585.

[5] De Vrij and Alluard, *Jahresb.* 1864, p. 445.

[6] *Pharm. Journ.* November 13, 1909.

acid, and becomes anhydrous at 125° and then melts at 172·8°. According to Hesse [1] anhydrous quinine is obtained in colourless needles, m.p. 174·4° to 175·4°, when sodium carbonate is added to quinine sulphate dissolved in warm water or when the trihydrate is heated during eight days in dilute alcohol at 30°. Anhydrous quinine is sparingly soluble in water (1 in 1960 at 15° (Hesse), 1 in 1667 at 20° (Sestini), 1 in 1750 at 25° (U.S.P.)), but readily so in alcohol (1 in 0·6 at 25°), ether (1 in 4·5 at 25°), chloroform (1 in 1·9 at 25°), or boiling benzene. Ammonia readily forms supersaturated solutions with quinine.[2] The alkaloid is lævorotatory, $[\alpha]_D - 158°$ at 15° in 99 per cent. alcohol (Rabe), or $0·894c - 169·38°$, where c is the weight in grammes of anhydrous quinine dissolved in 100 c.c. of alcohol.[3] The specific rotation of the alkaloid and of its salts varies considerably with the temperature and the solvent.[4] Solutions of quinine in certain oxygenated acids, e.g., sulphuric, phosphoric, and tartaric, fluoresce blue, but this is not shown by solutions in haloid acids,[5] and it disappears in presence of ferrocyanides.

In common with other alkaloids of this group, quinine has the property of forming molecular compounds with a variety of organic substances. Thus, with benzene and toluene it forms compounds of the formulæ, $B.C_6H_6$ and $B.C_7H_8$, respectively ; with phenol it gives the crystalline product, $B.C_6H_5OH$, and similar combinations with polyhydric phenols, ethers, aldehydes, and ketones are known. One of the most characteristic of these substances is cuprcine-quinine, a combination of the two alkaloids, which is readily obtainable from cuprea bark and was at first regarded as a new alkaloid and named " homoquinine " (see p. 147).

Salts. Quinine is a diacidic base forming both " neutral " and " acid " salts. The " neutral salts " (e.g., $B_2.H_2SO_4$), are faintly alkaline to litmus and strongly alkaline to methyl-orange. The alkaloid and its salts are intensely bitter to the taste. Three sulphates are known. Commercial quinine sulphate, $B_2.H_2SO_4$. $8H_2O$ (or $7H_2O$), is the " neutral " sulphate, and is obtained by neutralising the alkaloid (lacmoid or cochineal as indicator) with dilute sulphuric acid and recrystallising from boiling water, from which it separates in bulky masses of colourless, glistening needles which effloresce and lose their lustre on exposure to dry air, forming

[1] *Annalen*, 1890, **258**, 135.   *Cf.* Lenz, *Zeit. Anal. Chem.* 1888, **27**, 549.
[2] Duncan, *Pharm. Journ.* 1905, **74**, 438.
[3] Hesse, *Annalen*, 1875, **176**, 205.
[4] Oudemans, *ibid.* 1876, **182**, 44.
[5] *Cf.* however, Rabe and McMillan, *Annalen*, 1911, **382**, 360.

the dihydrate, $B_2.H_2SO_4.2H_2O$, m.p. 205°, which also results when the salt is exposed over sulphuric acid ; at 100° it becomes anhydrous and can be crystallised in this condition from boiling chloroform. The salt containing $7H_2O$ is sparingly soluble in water (1 in 720 at 25°, 1 in 30 at 100°), more soluble in alcohol (1 in 86 at 25°, 1 in 9 at 60°), readily soluble in a mixture of chloroform (2 parts) with alcohol (1 part), and very soluble in dilute acids. The solution in water is scarcely fluorescent, but is markedly so in dilute sulphuric acid. The hydrated sulphate is lævorotatory, $[\alpha]_D^{15} - 166\cdot36°$ in alcohol, or $- 233\cdot75°$ in the case of the anhydrous salt, $- 235°$ in 1 per cent. sulphuric acid (Tutin). The acid sulphate, $B.H_2SO_4.7H_2O$ (quinine disulphate), forms colourless, transparent, ortho-rhombic crystals, m.p. 160° (*decomp.*), $[\alpha]_D - 159\cdot1°$ (Tutin), which effloresce in air and turn yellow on exposure to light. It is soluble in water (1 in 8·5 at 25°) or alcohol (1 in 18 at 25°), and sparingly so in ether (1 in 1770 at 25°) or chloroform (1 in 920 at 25°). The aqueous solution is acid to litmus, neutral to methyl-orange, and markedly fluorescent.

The so-called tetrasulphate, $B.2H_2SO_4.7H_2O$, forms colourless prisms, and is exceedingly soluble in water, much less so in alcohol.

Quinine hydrochloride, $B.HCl.2H_2O$, closely resembles the neutral sulphate in appearance, and like it, effloresces in dry air, m.p. 158°–160° (dried at 100°), $[\alpha]_D^{17} - 133\cdot7°$ in water (Oudemans), $- 155\cdot8°$ (Tutin), soluble in water (1 in 18 at 25°), alcohol (1 in 0·6 at 25°), chloroform (1 in 0·8 at 25°), and sparingly in ether (1 in 240 at 25°). The aqueous solution is neutral to litmus and is not fluorescent except after the addition of sulphuric acid. The acid hydrochloride, $B.2HCl$, best obtained by treating a solution of the acid sulphate with barium chloride, crystallises in concentrically grouped needles and is very soluble in cold water (1 in 0·75). The hydrobromide, $B.HBr.H_2O$, resembles the hydrochloride, m.p. commences at 152° and ends at 200°, soluble in water (1 in 55 at 15°, Hesse), alcohol (1 in 0·67 at 25°), less so in chloroform, or ether. The aqueous solution is neutral and fluoresces only on addition of sulphuric acid. Quinine salicylate, $2(B.C_6H_5.COOH).H_2O$, forms colourless needles, m.p. 187° (*decomp.*), which slowly become pink in air. It is soluble in water (1 in 77 at 25°), alcohol (1 in 11 at 25°), or chloroform (1 in 37 at 25°).

The foregoing are the most important quinine salts used in medicine, but a large number of other salts have been used, *e.g.*, the tannate, formate, valerate, ethylcarbonate, lactate, cacodylate, etc.,

as well as amorphous double salts with iron tartrate and citrate, bismuth iodide, etc.

EXAMINATION OF COMMERCIAL QUININE SALTS.   The commercial salts invariably contain small amounts of the other cinchona alkaloids, especially cinchonidine and hydroquinine, and owing to their importance in medicine much attention has been given to devising tests which will ensure that the percentage of such impurities is small.   The total substitution of one alkaloid of this group for another, say, cinchonine for quinine, can be guarded against by the application of the thalleioquin (p. 136) and other tests, given under the respective alkaloids, whilst grosser impurities, such as added mineral matter and excess of water, would be detected by determination of the residue left on ignition, which should be negligible, and the loss on drying, which should not be greater than the water of crystallisation (14·5 to 15·2 per cent. in the commercial sulphate). Quinine dissolves in sulphuric or nitric acids practically without development of colour, and the production of coloured solutions under these conditions would indicate the addition of organic matter.

The ammonia test is chiefly relied on for the detection of excessive amounts of other cinchona alkaloids in quinine salts.   This is usually described for neutral quinine sulphate, but it can be applied to the other salts if these are first converted into neutral quinine sulphate.

Ammonia Test.[1]   The British Pharmacopœia (1914) gives this test in the following form for neutral quinine hydrochloride, the portion in italics is omitted for the neutral sulphate.   Two grammes of the salt are dissolved in a warm mortar in 20 c.c. of water at 60°, *1 grm. of powdered, non-effloresced sodium sulphate added, the mixture triturated,* cooled and allowed to stand at 15° for thirty minutes with occasional stirring, the crystals of quinine sulphate pressed and the expressed liquid filtered, 5 c.c. of this filtrate transferred to a dry test tube and brought to a temperature of 15°, yield, on gradual addition of 6 c.c. of solution of ammonia (sp. gr. 0·959) also at 15°, a precipitate, which redissolves on rotating the tube.

The United States Pharmacopœia (9th Rev.) gives this in the following form : Quinine sulphate is dried at 50° for two hours, and 1·8 grm. of the dried salt is shaken with 20 c.c. of water at 65° during thirty minutes, then cooled to 15°, and set aside at this temperature

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[1] For a detailed discussion of the application and utility of this test *see* Tutin, *Pharm. Journ.* 1909 [iv], **29, 600.**

with occasional agitation during two hours. It is then filtered through a filter paper 8 to 10 cm. in diameter. Five cubic centimetres of the filtrate are placed in a test tube and 7 c.c. of ammonia water at 15° (sp. gr. 0·958 at 25°) added all at once, when a clear liquid should be produced. For a digestion temperature of 16°, 7·5 c.c. and for 17°, 8 c.c. of ammonia water may be added.

Among other processes is the chromate method, which depends on the fact that quinine chromate is less soluble in water than the chromates of the accompanying alkaloids.[1] According to Hesse [2] and Lenz,[3] it gives high results for quinine owing to the inclusion of cinchonidine and hydroquinine. In Schäfer's oxalate test the quinine is precipitated as oxalate and the accompanying alkaloids estimated by rendering the filtrate alkaline and collecting and weighing the precipitate.[4] Lenz [3] states that this gives low but uniform results for the impurities present. Optical methods based on Oudemans' results in the investigation of the optical rotations of the cinchona alkaloids and their salts have been advocated by Hesse,[5] Byasson,[6] Koppeschaar,[7] Davies,[8] Léger [9] and others, but these methods have been little used, chiefly owing to the fact that the differences in rotation caused by even considerable quantities of impurities are small.[10] Critical *résumés* of methods of testing quinine sulphate have been published by Jungfleisch,[11] Lenz,[12] Howard [13] and Hille.[14]

Detection of Quinine. The various properties of quinine, which are described above, may be used for its identification, especially its bitter taste, and the fluorescence of certain of its salts in acid solution.

When bromine or chlorine water is added, drop by drop, to a faintly acid solution of a quinine salt until the reagent is present in

[1] André, *J. Pharm. Chim.* 1862, **41,** 341 ; De Vrij, *Arch. Pharm.* 1887, **225,** 1073 ; Schlickum, *ibid.* p. 128.

[2] *Pharm. Journ.* 1887 [iii], **17,** 585, 665 ; 1888 [iii], **18,** 582.

[3] *Zeit. Anal. Chem.* 1888, **27,** 575.

[4] *Arch. Pharm.* 1887, **225,** 64, 1033.

[5] *Berichte,* 1871, **4,** 693.

[6] *Journ. Pharm.* 1884 [v], **7,** 291.

[7] *Zeit. Anal. Chem.* 1885, **24,** 362.

[8] *Pharm. Journ.* 1884–85 [iii], **16,** 358.

[9] *J. Pharm. Chim.* 1904 [vi], **19,** 427.

[10] *Cf.* Paul, *Pharm. Journ.* 1885 [iii], **16,** 361 ; Hooper, *ibid.* 1886 [iii], **17,** 61 ; Hesse, *ibid.* 1887–88 [iii], **18,** 517 ; and Howard, *Watts'* *Dict. Chem.* vol. ii. p. 178.

[11] *Journ. Pharm.* 1887 [v], **15,** 5.

[12] *Zeit. Anal. Chem.* 1888, **27,** 549.

[13] *Loc. cit.* and *Pharm. Journ.* 1896 [iv], **3,** 505.

[14] *Arch. Pharm.* 1903, **241,** 54.

very slight excess, and then excess of ammonia, a characteristic deep green coloration is produced. This test, which is known as the " thalleioquin " reaction, is said to be given by 1 part of quinine in 20,000 of a solution.[1] It is also afforded by quinidine and cupreine, but not by cinchonine or cinchonidine. For work on the constitution and properties of " thalleioquin," *see* papers by Fühner,[2] Comanducci[3] and Christensen,[4] and for investigations on the action of halogens on quinine and other cinchona alkaloids papers by Rohde and Meissner[5] and Weller.[6]

Quinine is more soluble in ether and in ammonia solution than the other cinchona alkaloids, and its oxalate and chromate are less soluble in water. It affords a series of periodides of which that known after its discoverer as " herepathite," $B_4.3H_2SO_4.2HI.I_4.6H_2O$, is characteristic. This is prepared by dissolving neutral quinine sulphate in alcohol, adding the calculated quantity of sulphuric acid, then heating to the boiling-point and adding the requisite quantity of iodine dissolved in alcohol. The crystals which separate are washed with cold 70 per cent. alcohol and recrystallised from boiling alcohol, when they separate in tablets or leaflets, which are golden-green by reflected light, very pale olive-green by transmitted light, and polarise light like tourmaline.[7]

Quinidine (*Conquinine*), $C_{20}H_{24}O_2N_2$. This isomeride of quinine is contained in small quantity in most cinchona barks, but especially in *C. pitayensis, C. amygdalifolia* and *C. Calisaya*, which sometimes contain as much as 3 per cent.[8]

It occurs in the mother liquors from the preparation of quinine sulphate, and from the mixture of alkaloids, known as " quinoidine," obtained by precipitating these liquors with caustic soda, it may be obtained with cinchonidine by extraction with ether. The cinchonidine is removed by dissolving the residue in dilute sulphuric acid, neutralising with ammonia solution and precipitating with sodium potassium tartrate. From the filtrate quinidine is separated as the hydriodide by precipitation with potassium iodide solution.[9] From this it is removed and recrystallised from boiling alcohol.

[1] *Cf.* Hart, *Journ. Soc. Chem. Ind.* 1921, **40**, 72T.
[2] *Arch. Pharm.* 1906, **244**, 602.
[3] *Abstr. Chem. Soc.* 1910 [i], 581 ; 1911 [i], 317.
[4] *Ber. Deut. Pharm. Ges.* 1915, **25**, 256 ; 1916, **26**, 249.
[5] *Berichte*, 1914, **57**, 1507.
[6] *Ibid.* 1921, **54**, 230.
[7] Jörgensen, *Journ. prakt. Chem.* 1876 [ii], 14, 230.
[8] Hesse, *Annalen*, 1874, **174**, 338.
[9] Hesse, *ibid.* 1868, **146**, 358 ; 1873, **166, 236**.

Quinidine crystallises from ordinary alcohol with 2·5 and from dry alcohol with 1 mol. of the solvent in prisms, from dry ether with $\frac{1}{3}$ mol. ether in trimetric tablets, and from boiling water with $1\frac{1}{2}H_2O$ in leaflets. Freed from solvents of crystallisation or obtained in anhydrous crystals from benzene, it melts at 171·5°, and has the following solubilities : water, 1 in 2000 at 15° ; ether, 1 in 35 at 10° ; alcohol, 1 in 26 of 80 per cent. at 20° ; it is sparingly soluble in chloroform and less so in light petroleum. It is dextrorotatory, $[\alpha]_D + 274\cdot7°$ in alcohol 1 vol., chloroform 2 vols. (Lenz), $+ 243\cdot5°$ (Rabe). The sulphate and the salts of other oxygenated acids show a blue fluorescence, especially in dilute sulphuric acid.

Quinidine is alkaline in solution and behaves as a diacidic base forming two series of salts. The neutral sulphate, $B_2.H_2SO_4.2H_2O$, crystallises from hot water in colourless prisms, soluble in water (1 in 98 to 100 at 15°, or 1 in 7 at 100°), more so in alcohol or chloroform, and scarcely in ether. It is dextrorotatory, $[\alpha]_D + 184\cdot17°$ in chloroform. The acid sulphate, $B.H_2SO_4.4H_2O$, forms hair-like, colourless needles, soluble in 8·7 parts of water at 10°. The neutral hydrochloride, $B.HCl.H_2O$, m.p. 258°–259° (*dry, decomp.*), $[\alpha]_D^{20} + 200°$ in water, forms asbestos-like prisms, easily soluble in alcohol or hot water, less so in cold water (1 in 62·5 at 10°). The acid hydrochloride, $B.2HCl.H_2O$, forms prisms, readily soluble in alcohol, sparingly in water, chloroform, or hydrochloric acid. The neutral hydriodide, $B.HI$, is deposited as a crystalline powder when potassium iodide is added to a neutral aqueous solution of a quinidine salt, and is the form in which the alkaloid is usually isolated and estimated, since it is less soluble in water (1 in 1250 at 15°, 1 in 1270 at 10°) than the hydriodides of the other cinchona alkaloids.

Detection and Estimation. Quinidine gives the thalleioquin reaction (p. 136), and is fluorescent in dilute sulphuric acid. Unlike quinine, it is dextrorotatory, gives a sparingly soluble hydriodide and a neutral sulphate soluble in water or chloroform.

Quinicine (*Quinotoxine*), $C_{20}H_{24}O_2N_2$. This alkaloid was isolated by Howard[1] from cinchona bark, but had been prepared previously by Pasteur[2] by heating acid quinine sulphate, and subsequently by Hesse[3] in a similar manner from quinidine. It is also formed by

[1] *Journ. Chem. Soc.* 1871, **24**, 61 ; 1872, **25**, 101.
[2] *Jahresberichte*, 1853, p. 473. *Cf.* Howard and Chick, *Pharm. Journ.* 1917, **99**, 143.
[3] *Annalen*, 1875, **178**, 245 ; 1888, **243**, 148.

heating quinine in dilute acetic acid or water.[1] It is purified by conversion into (1) the oxalate, $B_2.H_2C_2O_4.9H_2O$, small prisms, m.p. 149°, which is insoluble in water, and, unlike that of quinine, can be recrystallised from chloroform or alcohol ; or (2) the hydrochloride, B.HCl, which forms aggregates, m.p. 179°–180°, or leaflets, m.p. 180°–182° ; $[\alpha]_D + 16·26°$ or $+ 13·7°$.[2]

The base is a bitter alkaline, yellow oil, $[\alpha]_D + 38° 40'$ in chloroform,[3] slightly soluble in water, easily in alcohol or ether. It gives the thalleioquin reaction, but its salts are not fluorescent in solution. Quinicine was long regarded as distinct from quinotoxine, but their identity was finally proved by von Miller and Rohde.[4]

In addition to quinicine the following isomerides of quinine and quinidine have been prepared and described. None of them have been found to occur naturally.

Other Isomerides of Quinine, $C_{20}H_{24}O_2N_2$

Name	Method of formation	Crystalline form	Optical rotation $[\alpha]_D$
*Pseudo*quinine (Skraup, *Monats.* 1893, **14**, 446)	These two isomerides are formed together when hydroiodoquinine dihydriodide is heated with potash in alcohol, and are separated by fractional crystallisation of their oxalates	Prisms, m.p. 190°–191°	− 164·4° in alcohol
*Iso*quinine (Lippmann and Fleissner, *Monats.* 1891, **12**, 332 ; 1893, **14**, 554. *Cf.* Böttcher, 1911, **32**, 793)		Minute needles, m.p. 185° (L. & F.) ; 189° (Böttcher)	− 186·6° in alcohol
*Iso*quinidine (Pfannl, *Monats.* 1911, **32**, 241)	By solution of quinidine sulphate in sulphuric acid	Long needles, m.p. 142°	$[\alpha]_j − 9°$

Apoquinine, $C_{19}H_{22}O_2N_2.2H_2O$. This substance, isomeric with cupreine (p. 146), is produced from quinine together with methyl chloride by the action of strong hydrochloric acid.[5] It also results

[1] Biddle, *Berichte*, 1912, **45**, 526. *Cf.* Miller, Rohde, and Fussenegger, *ibid.* 1900, **33**, 3214.
[2] Jacobs and Heidelberger, *Journ. Amer. Chem. Soc.* 1919, **41**, 817.
[3] Howard and Perry, *Journ. Soc. Chem. Ind.* 1909, **28**, 53.
[4] *Berichte*, 1900, **33**, 3214.
[5] Hesse, *Annalen*, 1880, **205**, 323.

when cupreine is heated with this reagent at 140°.[1] The base crystallises in needles, m.p. 210° (*decomp.*), $[\alpha]_D - 178 \cdot 1°$ in 97 per cent. alcohol. Its salts are generally amorphous.

With acetic anhydride it gives an amorphous diacetyl derivative, which resembles quinine, but not apoquinine, in giving the thalleioquin reaction and in being fluorescent in dilute sulphuric acid solution. The base is unsaturated, readily combines with 1 mol. of a halogen acid, and has the properties of a phenol.

Cinchonine, $C_{19}H_{22}ON_2$. This alkaloid is almost invariably present in cinchona and cuprea barks, but the quantity is usually small. One of the best sources is *Cinchona micrantha* bark. The alkaloid occurs as the sulphate in the crude mother liquors from which quinine sulphate has been crystallised. The mixed alkaloids contained in these are precipitated by the addition of caustic soda solution, extracted with ether to remove quinidine and cinchonidine and the insoluble residue boiled with successive small quantities of alcohol, from which cinchonine crystallises on cooling. The crude alkaloid is neutralised with dilute sulphuric acid, and the sulphate recrystallised from boiling water.

Cinchonine is precipitated from aqueous solutions of its salts, on addition of an alkali in an amorphous condition, but becomes crystalline on standing. It separates from alcohol in rhombic prisms, m.p. 264°, $[\alpha]_D^{17} + 229°$ in dry alcohol, or $+ 234° 33'$ in alcohol 1 vol., chloroform 2 vols., is sparingly soluble in water (1 in 3810 at 10°, 1 in 3670 at 20°), more so in alcohol, sp. gr. 0·852 (1 in 140 at 10°, 1 in 125·7 at 20°, 1 in 28 of boiling alcohol), ether, sp. gr. 0·7305 (1 in 371 at 10°), or amyl alcohol (1 in 109 at 15°, or 1 in 22 boiling).

It behaves as a diacidic base, and gives two series of salts. The neutral sulphate, $B_2 . H_2SO_4 . 2H_2O$, forms rhombic crystals, m.p. 200° (*dry, decomp.*), readily soluble in 80 per cent. alcohol (1 in 5·8 at 11°), moderately so in water (1 in 65·5 at 13°), $[\alpha]_D + 193·29° - 0·374c$, where $c =$ grammes of alkaloid per 100 c.c. of 97 per cent. alcohol, or $+ 133°$ in chloroform. The acid sulphate, $B . H_2SO_4 . 4H_2O$, colourless octahedral crystals readily soluble in alcohol (1 in 0·9 at 14°), or water (1 in 0·46 at 14°). The neutral hydrochloride, $B . HCl . 2H_2O$, m.p. 217°–218° (*dry*), forms monoclinic crystals, soluble in 22 parts of cold water or 1 part of cold alcohol, $[\alpha]_D^{25} + 133°$ in chloroform (Rabe).

Detection. Cinchonine, unlike quinine and quinidine, does not

[1] Hesse, *Annalen*, 1885, **230**, 65.

give the thalleioquin reaction (p. 136), is sparingly soluble in ether, and is not fluorescent in dilute sulphuric acid. From cinchonidine it differs in being sparingly soluble in ether and is dextrorotatory.

Homocinchonine has been shown to be impure cinchonine.[1]

Cinchonidine, $C_{19}H_{22}ON_2$. This isomeride of cinchonine occurs in most varieties of cinchona bark, but especially in *C. succirubra.*

Preparation. The ethereal solution obtained as described for the preparation of quinidine (p. 136), is shaken with dilute hydrochloric acid, the acid liquid separated, neutralised with ammonia, and sodium potassium tartrate added, to precipitate cinchonidine tartrate. The base is recovered from this by dissolving in dilute acid, adding ammonia solution in excess, and crystallising the precipitate from alcohol. The crude alkaloid is then converted into the neutral sulphate, and this recrystallised by dissolving it in twenty-five times its weight of boiling water and cooling to 35°. The crystals which separate at this temperature after the third crystallisation are generally free from impurities, and cinchonidine may be regenerated from them as described already. This process may also be used to purify commercial cinchonidine sulphate.[2]

Cinchonidine crystallises in large trimetric prisms, m.p. 207·2° (Lenz), 202·4° (Hesse), $[\alpha]_D - 107·9°$ in alcohol 1 vol., chloroform 2 vols. (Lenz), $- 111°$ in alcohol (Rabe) ; is sparingly soluble in water (1 in 5263 at 11·5° (Skraup)) ; more soluble in alcohol (1 in 303 of alcohol, sp. gr. 0·935 at 11·5° (Skraup), 1 in 16·3 of 97 per cent. alcohol at 13° (Hesse) ; or ether (1 in 1053 of dry ether at 11·5° (Skraup), 1 in 188 of ether, sp. gr. 0·72 at 15° (Hesse)). Cinchonidine is not fluorescent in dilute sulphuric acid solution, and does not give the thalleioquin reaction. It is a diacidic base, and yields two series of salts. The neutral sulphate, $B_2.H_2SO_4$. m.p. 205° (*dry*) forms monoclinic prisms with $6H_2O$ from cold water, or with $3H_2O$ from hot water, and is soluble in alcohol (1 in 72 at 25°), or water (1 in 63 at 25°). The trihydrated sulphate is official in the United States Pharmacopœia. The acid sulphate, $B.H_2SO_4.5H_2O$, is easily soluble in water, whilst the " tetrasulphate," $B.2H_2SO_4.H_2O$, dissolves slowly in water. The neutral hydrochloride, $B.HCl.H_2O$,

[1] Skraup, *Monats.* 1899, **20**, 579. *Cf.* Hesse, *Annalen*, 1888, **243**, 149 ; 1893, **276**, 103.

[2] Hesse, *Annalen*, 1880, **205, 196.**

m.p. 242° (*dry*), $[\alpha]_D - 117 \cdot 6°$ (anhydrous salt, $c = 1 \cdot 214$ in water), forms monoclinic double pyramids, or silky prisms with $2H_2O$, from its saturated aqueous solution. The dry salt is moderately soluble in water (1 in 38·5 at 10°), or ether (1 in 325 at 10°), readily in chloroform. The acid hydrochloride, $B.2HCl.H_2O$, forms large monoclinic prisms very easily soluble in water or alcohol. The tartrate, $B_2.H_2C_4H_4O_6.2H_2O$, is a crystalline precipitate, sparingly soluble in water (1 in 1265 at 10°), almost insoluble in sodium potassium tartrate solution, and is the form in which the alkaloid is usually estimated (*see* p. 129).

Detection. Cinchonidine is readily distinguished from quinine and quinidine by not being fluorescent in dilute sulphuric acid, and by not giving the thalleioquin reaction. It differs from cinchonine in being lævorotatory, in being more soluble in ether, and in the sparing solubility of its tartrate.

Homocinchonidine, $C_{19}H_{22}ON_2$, is stated by Hesse to accompany cinchonidine in many cinchona barks, but especially in *C. rosulenta*,[1] and to be produced along with apocinchonidine (*see* Table, p. 143) by the action of hydrochloric acid or diluted sulphuric acid on cinchonidine at 140°.[2] The base crystallises from alcohol in thick, short prisms, m.p. 207·6°, 201° (Dobbie), $[\alpha]_D - 107 \cdot 3°$ in 97 per cent. alcohol, soluble in chloroform or alcohol (1 in 20·5 of 97 per cent. alcohol at 13°), sparingly in ether (1 in 216 at 15°). The neutral sulphate, $B_2.H_2SO_4.6H_2O$, crystallises from hot water in thin needles, is soluble in 69 parts of water at 22°, and has $[\alpha]_D - 137 \cdot 96°$ in dilute hydrochloric acid. Homocinchonidine does not give the thalleioquin reaction (p. 136), and its solutions in dilute sulphuric acid are not fluorescent. In view of the similarity of its constants to those of cinchonidine it is not surprising that the two alkaloids are regarded by some authorities as identical.

ISOMERIDES OF CINCHONINE. In addition to the naturally occurring cinchonidine, numerous other isomerides produced by the action of various reagents on these two alkaloids have been described. A summary of the chief data recorded regarding the more definitely established isomerides is given in the table on p. 143.

One of the most interesting of these is cinchonicine (cinchotoxine) first prepared by Pasteur and now of considerable importance in connection with the investigation of the constitution of the cinchona alkaloids (*cf.* p. 148). Its formation from cinchonine and

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[1] *Annalen*, 1880, **205**, 203.
[2] *Ibid.* 1880, **205**, 307 ; 1883, **243**, 148 ; 1890, **258**, 142.

cinchonidine has been investigated fully by Rabe and McMillan,[1] and by Biddle and co-workers.[2]

A second isomeride, α-*iso*cinchonine was re-examined by Rabe and Böttcher,[3] who confirmed for it the constitutional formula suggested by Königs.[4]

A number of the other isomerides have been examined in recent years by Léger,[5] who has shown that the " δ-cinchonine " described by Jungfleisch and Léger in 1894 is a mixture of two isomerides now named α-*cinchonhydrine* (m.p. 144·4°, $[\alpha]_D$ for B.2HCl in water $+ 196·8°$), and β-*cinchonhydrine* (m.p. 155·8°, $[\alpha]_D$ for B.2HCl in water $+ 106°$), the former being probably identical with Langer's δ-cinchonine.[6] Several of these isomerides are produced from α- and β-hydroxycinchonines and hydroxycinchonidine, as well as from the two natural alkaloids.[7] Two further isomerides have been obtained by the action of bromine on cinchonicine and subsequent hydrolysis by water.[8]

Cinchotine (*Hydrocinchonine*, *Cinchonifine*, *ψ-Cinchonine*), $C_{19}H_{24}ON_2$. This alkaloid occurs in most varieties of cinchona bark, and is a common constituent of commercial cinchonine,[9] from which it may be prepared by crystallising the alkaloid from alcohol and oxidising the more soluble fraction with permanganate at 0° C., in presence of sulphuric acid. The cinchotine can then be precipitated from the filtrate with ammonia.[10] It is, however, much more conveniently prepared by catalytic hydrogenation of cinchonine[11] (p. 145).

Cinchotine crystallises in prisms, m.p. 268°–269°, $[\alpha]_D^{14} + 190°$ (Rabe), $+ 204·5°$ in alcohol (Hesse), less soluble in chloroform or alcohol (1 in 221·5) than cinchonine. The base is diacidic and forms two series of salts ; the neutral sulphate, $B_2.H_2SO_4.11H_2O$, forms fine needles, m.p. 194·8°–195° (*dry*), soluble in water (1 in 37·6 at 12°).

[1] *Berichte*, 1910, **43**, 3308.

[2] *Ibid.* 1912, **45**, 526 ; *Journ. Amer. Chem. Soc.* 1915, **37**, 2082 ; *ibid.* 1917, **39**, 968.

[3] *Berichte*, 1917, **50**, 127.

[4] *Annalen*, 1906, **347**, 143.

[5] *Compt. rend.*, 1918, **166**, 76, 469 ; 1919, **169**, 797.

[6] *Monats.* 1901, **22**, 151, 157.

[7] Léger, *Compt. rend.*, 1918 ; **166**, 255, 903 ; 1919, **168**, 404 ; 1919, **169**, 67 ; Jungfleisch and Léger, *Ann. Chimie*, 1920 [ix], 1459.

[8] Rohde and Meissner, *Berichte*, 1914, **47**, 1507.

[9] Hesse, *Annalen*, 1873, **166**, 256 ; 1898, **300**, 46. *Cf.* Forst and Böhringer, *Berichte*, 1881, **14**, 436 ; 1882, **15**, 520.

[10] For other methods *see* Hesse, *Annalen*, 1898, **300**, 44 ; and Pum, *Monats.* 1895, **16**, 68.

[11] Heidelberger and Jacobs, *Journ. Amer. Chem. Soc.* 1919, **41**, 817.

Name	Synonym	Method of formation	Properties	References
*iso*Cinchoni-dine		By solution of cin-chonidine sulphate in sulphuric acid .	Leaflets, m.p. 235°, 252°(Paneth) $[a]_D - 128°$	Hesse, *Annalen,* 1888. **243,** 149. Paneth, *Monats.* 1911, **32,** 257
β-Cinchoni-dine		By the action of alco-holic potash on hydro-iodocinchonidine	Tabular crystals, m.p. 244°, lævorotatory	Neumann, *Monats.* 1892. **13,** 655
γ-Cinchoni-dine		By heating cinchoni-dine trihydriodide with aqueous silver nitrate	m.p. 238°, lævorotatory	
*apo*Cin-chonidine		By heating cinchoni-dine with hydrochloric acid at 140°–150°	Leaflets, m.p. 225° $[a]_D - 129·2°$	Hesse, *Annalen,* 1880, **205,** 327
*allo*Cin-chonine	β-Cin-chonine *apo*Cin-chonine γ-Cin-chonine *apoiso*Cin-chonine *isoapo*Cin-chonine	By heating hydroiodo-cinchonine with alco-holic potash	Needles, m.p. 214°–216°, 218°–220° (Dobbie) $[a]_D + 164·8°$	Skraup and col-laborators, *Monats.* 1899, **20,** 571 ; 1900, **21,** 512, 535, 558 ; 1901, **22,** 171, 191, 253, 1083 1097,1103 ; 1902, **23,** 443, 455 ; 1903. **24,** 311; 1904, **25,** 894.
" δ-Cin-chonine " $C_{18}H_{22}ON_2$		By heating hydrobro-mocinchonine with alcohol	m.p. 150° $[a]_D + 125·2°$	
ϵ-Cin-chonine		Formed with δ-cin-chonine when alco-holic potash is used	m.p. 150° $[a]_D + 58·3°$	
a-*iso*Cin-chonine	Cinchoni-line Dia*po*cin-chonine	By heating cinchonine sulphate with sulphuric acid	pseudo-rhombic prisms, m.p. 126° $[a]_D + 49·74°$	Lowen-haupt, *ibid.* 1898, **19,** 461. Kaas, *ibid.* 1904, **25,** 1145 ; 1905, **26,** 296. Roques, *Ann. Chim. Phys.* 1897 [vii], **10,** 234. von Miller and Rohde, *Berichte,* 1900, **33,** 3214
β-*iso*Cin-chonine	Cinchoni-gine Dia*po*cin-chonine	Formed with a-*iso*cin-chonine as above	Prisms, m.p. 126°–127° $[a]_D - 54·02°$	
Cinchoni-cine	Cincho-toxine	By heating cinchonine or cinchonidine with acetic acid, sulphuric acid, or glycerol	Needles, m.p. 58°–59° $[a]_D + 46·5°$ $+ 49·62°$ (Rabe)	
a-*iso*Cin-chonicine		By heating a-*iso*cin-chonine sulphate at 140°		
a-*iso*-ψ-Cin-chonicine		Ditto	Amorphous m.p. 73°–74°	
β-*iso*-ψ-Cin-chonicine		By heating β-*iso*cin-chonine sulphate		
*tauto*Cin-chonine		By action of potash on cinchonine bromide	m.p. 252·5° $[a]_D + 209·4°$	

The hydrochloride, $B.HCl.2H_2O$, m.p. $216.5°$, $220°–221°$ (*dry, decomp.*), $[\alpha]_D + 155°$ to $159°$),[1] occurs in small needles, and the platinichloride, $B_2.2HCl.PtCl_4$, in orange-red needles, sparingly soluble in water. On boiling with acetic acid, it is converted into *dihydrocinchonicine*, a viscous yellow oil, $[\alpha]_D^{23°} + 8.8°$ in alcohol, which gives a crystalline benzoyl derivative, m.p. $121°–122°$.

Hydrocinchonidine (*Cinchamidine*), $C_{19}H_{24}ON_2$. This alkaloid was isolated by Forst and Böhringer [2] from the bark of *Cinchona Ledgeriana*, but has since been found in many varieties of cinchona. It may be obtained from commercial cinchonidine sulphate by fractional precipitation with sodium tartrate, the hydrocinchonidine tartrate occurring in the last fractions ; these are treated with potassium permanganate solution, to destroy cinchonidine ; the hydro-base can then be regenerated and crystallised from hot alcoholic solution by gradual addition of water. It is best prepared by catalytic hydrogenation of cinchonidine [3] (p. 145).

Hydrocinchonidine crystallises in six-sided leaflets, m.p. $229°$, $[\alpha]_D - 98.4°$ in alcohol, is insoluble in water and only slightly soluble in other solvents except alcohol. The salts exhibit no fluorescence in solution nor do they show the thalleioquin reaction (p. 136). The base is diacidic and forms salts similar to those of quinine and cinchonine : the neutral sulphate, $B_2.H_2SO_4.7H_2O$, needles soluble in water (1 in 57 at $10°$) ; the acid sulphate, $B.H_2SO_4.4H_2O$, leaflets, slightly soluble in water. The hydrochloride, $B.HCl.2H_2O$, m.p. $202°–203°$ (*dry*), $[\alpha]_D - 89.4°$ (anhydrous salt in water $c = 1.19$), short six-sided prisms, very soluble in water or alcohol.

Hydroquinine, $C_{20}H_{26}O_2N_2.2H_2O$. This base was isolated by Hesse [4] from the bark of *Cinchona Ledgeriana* and is a common constituent to the extent of 1 to 2 per cent. of commercial sulphate of quinine. It can be prepared by repeatedly recrystallising the latter as acid sulphate and treating the final mother liquor with potassium permanganate at $0°$ C., when the remaining quinine is destroyed. The hydro-base may then be obtained by the addition of sodium hydroxide solution and extraction with ether. The demand for hydroquinine for use as such in medicine and as a raw material for the preparation of hydrocupreine to be used in making

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[1] Heidelberger and Jacobs, *Journ. Amer. Chem. Soc.* 1919, **41**, 817.
[2] *Berichte*, 1881, **14**, 1270 ; Hesse, *ibid.* 1683, *Annalen*, 1882, **214**, 1.
[3] Skita and Nord, *Berichte*, 1912, **45**, 3312.
[4] *Berichte*, 1882, **15**, 854 ; *Annalen*, 1887, **241**, 257.

the higher homologues of hydroquinine by alkylation, has become so considerable in recent years, that much attention has been given to its manufacture from quinine, the usual method being catalytic hydrogenation. As an example the following may be quoted from British Patent 3948 of 1912 : " One part of palladium black is added to a solution of 250 parts of quinine sulphate in 1,400 parts of water and 40 parts of sulphuric acid, and the mixture shaken with hydrogen under a low pressure, until it is stable towards permanganate ; after filtration the solution is neutralised while hot, when hydroquinine sulphate will at once crystallise in the form of slender needles." Catalytic hydrogenation is equally applicable to the other cinchona alkaloids and their derivatives, such as the isomeric keto-bases (quinicines or quinatoxins), and esters such as quinine ethyl carbonate, and numerous applications of the method have been described in this connection.[1]

It crystallises from ether or chloroform in needles, m.p. 172·3° (dry), $[\alpha]_D^{20°} - 142\cdot2°$ in alcohol, is easily soluble in ether, alcohol, chloroform, acetone, or ammonia solution. Hydroquinine gives the thalleioquin reaction (p. 136), solutions in dilute sulphuric acid are fluorescent, but is distinguished from quinine by its resistance to permanganate.

It is a diacidic base and furnishes two series of salts resembling those of quinine. The neutral sulphate, $B_2.H_2SO_4.6H_2O$, occurs in short prisms, insoluble in ether, sparingly soluble in chloroform, and moderately so in water (1 in 348 at 15°), $[\alpha]_D^{15°} - 220°$ in hydrochloric acid (4 mols.). The acid sulphate, $B.H_2SO_4.3H_2O$, forms long needles, easily soluble in water or alcohol. The hydrochloride, $B.HCl$, has m.p. 235°–240° (dry), and $[\alpha]_D^{24°} + 140\cdot6°$, in water. The alkaloid forms a crystalline benzoyl derivative, m.p. 102°–107° ; with methyl iodide it gives a methiodide, which crystallises with one molecule of methyl alcohol. It readily forms crystalline molecular compounds with cinchonidine, quinidine and cupreine, and by heating its acid sulphate at 140°, or by Miller and Rohde's process, it is transformed into the isomeric *hydroquinicine* (hydroquinotoxine) sulphate, m.p. 174°. On demethylation it furnishes hydrocupreine (p. 147).

[1] German Patents, 251,936, 253,357 (*Chem. Soc. Abstr.* 1913 [i], 85), 306,939 (*ibid.* 1918 [i], 546) ; *also* Skita and co-workers, *Berichte*, 1911, **44**, 2866 ; 1912, **45**, 3312, 3588 ; 1916, **49**, 1597 ; Kaufmann and Huber, *ibid.* 1913, **46**, 2913. Freund and Bredenburg, *Annalen*, 1914, **407**, 43 ; Jacobs and Heidelberger, *J. Amer. Chem. Soc.* 1919, **41**, 817 ; 1922, **44**, 1098. For a useful general account of catalytic hydrogenation, *see* Houben-Weyl, *Die Methoden der organischen chemie*, 2nd ed. 1922, Vol. II.

Hydroquinidine (*Hydroconquinine*), $C_{20}H_{26}O_2N_2 . 2\frac{1}{2}H_2O$.   This base occurs in the quinidine of commerce, and was isolated from this source by Forst and Böhringer [1] by the method employed for the preparation of hydroquinine from commercial sulphate of quinine, or by repeated crystallisation of commercial quinidine sulphate or hydrochloride from water or alcohol when the hydro-quinidine salt remains in the mother liquors,[2] but is best prepared by catalytic reduction of quinidine (p. 145).[3]   The purified alkaloid forms thick tablets from ether or long needles from alcohol, m.p. 166°–167°, $[\alpha]_D + 230°$, gives the thalleioquin reaction (p. 136), and its sulphate is fluorescent in water or dilute sulphuric acid.   The sulphate, $B_2 . H_2SO_4 . 12H_2O$, forms thick bottle-shaped crystals or fine needles with $2H_2O$, soluble in 92·3 parts of water at 16°.   The hydrochloride, B.HCl, m.p. 273°–274° (*decomp., dry*), $[\alpha]_D^{26} + 183·9°$, prismatic plates, easily soluble in water ;   the platinichloride, $B . 2HCl . PtCl_4$, short, orange-coloured needles.

The base can be transformed into hydroquinicine (p. 145), and cn demethylation yields dihydrocupreidine [3] (p. 148).

Cupreine, $C_{19}H_{22}O_2N_2 . 2H_2O$.   Cupreine is contained, together with quinine, in the bark (cuprea bark) of *Remijia pedunculata*, a plant closely related to, though distinct from, the cinchonas.[4]

Preparation.—The total alkaloids of cuprea bark are dissolved in dilute sulphuric acid, and the solution exactly neutralised with caustic soda, when the sulphate of a compound of cupreine and quinine called *homoquinine* (*see* p. 132), crystallises.   This is dis-solved in dilute sulphuric acid, excess of soda added and the liquid shaken with ether, which removes quinine, leaving the cupreine in the alkaline solution.   On neutralising the latter with dilute sul-phuric acid, cupreine sulphate crystallises out, from which the base may be obtained by dissolving the salt in dilute sulphuric acid, adding ammonia and crystallising the precipitate from alcohol.

Cupreine crystallises in concentrically grouped prisms, becomes anhydrous at 120°, and then melts at 198°, $[\alpha]_D^{17} - 175·5°$ in *dry* alcohol, $- 163° 45'$ in aqueous alcohol.   It is sparingly soluble in ether or chloroform, readily in alcohol or solutions of caustic alkalis, but not in ammonia, and gives the thalleioquin reaction (p. 136).

[1] *Berichte*, 1881, **14,** 1954 ; 1882, **15,** 520, 1656.

[2] Hesse, *ibid.* 1882, **15,** 855, 3010.

[3] Heidelberger and Jacobs, *Journ. Amer. Chem. Soc.* 1919, **41,** 817.

[4] Paul and Cownley, *Pharm. Journ.* 1881, **12,** 497 ; 1884 [iii], **15,** 221, 401.   *Cf.* Howard and Hodgkin, *ibid.* 1881 [iii], 12, 528, and Whiffen, *ibid.* 1881, **12,** 497 ; Hesse, *Annalen,* 1885, **230,** 57.

Cupreine is a diacidic base and yields two series of salts : the neutral sulphate, $B_2.H_2SO_4$, colourless anhydrous needles,[1] soluble in 813 parts of water at 17° ; the acid sulphate, $B.H_2SO_4.H_2O$, crystallises in prisms and is soluble in 73·4 parts of water at 17°. On methylation cupreine is converted into quinine, but the latter on demethylation yields apoquinine (p. 138), which is also formed when cupreine is heated with halogen acids.

Homoquinine (*Cupreine-quinine*). When cupreine and quinine in chemically equivalent quantities are dissolved in dilute sulphuric acid, the mixture precipitated with ammonia, and the precipitate dried and crystallised from ether, a molecular combination of the two alkaloids, $C_{19}H_{22}O_2N_2.C_{20}H_{24}O_2N_2.4H_2O$, is obtained which has been called homoquinine.[2] It crystallises in needles, plates or prisms, m.p. 177° (*dry*), $[\alpha]_D - 235·6°$ (in hydrochloric acid) becomes anhydrous at 125°, is easily soluble in chloroform or alcohol, less so in ether, and gives fluorescent solutions in dilute sulphuric acid. It behaves as a diacidic base and forms crystalline salts. The neutral sulphate, $B.B'.H_2SO_4.6H_2O$, forms short hexagonal prisms sparingly soluble in water, easily in boiling alcohol, insoluble in chloroform or ether. Homoquinine is resolved into its components by solution in dilute acids and addition of caustic soda solution, which dissolves the cupreine and precipitates the greater part of the quinine.

Hydrocupreine, $C_{19}H_{24}O_2N_2$. This alkaloid does not occur naturally, so far as is known, but can be produced by demethylating dihydroquinine (*see* p. 144) by boiling with halogen acids,[3] or by reducing cupreine.[4] It crystallises from dilute alcohol in minute needles or from a mixture of chloroform and benzene in warty masses, m.p. 204° (G. and H.), 230° (H. and J.), readily soluble in chloroform, alcohol, hot benzene, and much less so in ethyl acetate, insoluble in light petroleum, $[\alpha]_D^{20} - 155·5°$ or 154·8° (G. and H.), $[\alpha]_D^{23} - 148·7°$ (H. and J.) in dry alcohol. The hydrochloride, $B.HCl$, m.p. 280° (*decomp.*), $[\alpha]_D^{22·5} - 132·3°$ in water, crystallises in needles ; the dihydrobromide, $B.2HBr.2H_2O$, leaf-like masses of prisms, m.p. 180°–190°, and the nitrate, $B.HNO_3$, in flattened needles, m.p. 220°–222°. On methylation the base yields hydro-

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[1] Howard and Chick, *Journ. Soc. Chem. Ind.* 1909, **28,** 53.

[2] Howard and Hodgkin, *Trans. Chem. Soc.* 1882, **41,** 61. *Cf.* Paul and Cownley, *Pharm. Journ.* 1881 [iii], **12,** 497 ; 1884 [iii], **15,** 402.

[3] Hesse, *Annalen*, 1887, **241,** 281 ; Heidelberger and Jacobs, *Journ. Amer. Chem. Soc.* 1919, **41,** 817.

[4] Giemsa and Halberkann, *Berichte*, 1918, **51,** 1325 ; Kelber, *ibid.* 1916, **49,** 55.

quinine, and a series of homologues of quinine has been prepared from it (*cf.* p. 171), *e.g.*, (1) *Ethylhydrocupreine hydrochloride* ("optoquin"), B.HCl, rhombic crystals, m.p. 252°–254°, $[\alpha]_D^{21} - 123 \cdot 6°$ in water; the hydrobromide, m.p. 258°–259°; the methiodide, pale yellow plates, m.p. 195°–196°, $[\alpha]_D^{21 \cdot 5} - 113°$.[1] The base itself is a white powder, m.p. 122°, $[\alpha]_D^{20} - 144 \cdot 3°$ in dry alcohol,[2] or crystallised from toluene, m.p. 123°–128°, $[\alpha]_D^{25} - 136 \cdot 2°$.[1] (2) *sec*-Octylhydrocupreine dihydrochloride ("vuzin"), $B.2HCl.2H_2O$, pale yellow sheaves or rosettes of needles, m.p. 190°–195°.[3]

On treatment by Miller and Rohde's general process, hydrocupreine is converted into hydrocupreinotoxine (hydrocupreicine), and this, too, can be alkylated, giving a series of homologues of dihydroquinicine, *e.g.*, "optoquinotoxin" (ethyl ether)," eucupinotoxin" (amyl ether), etc.

Hydrocupreidine, $C_{19}H_{24}O_2N_2.xH_2O$. This base, isomeric with the foregoing, is only obtainable by demethylating hydroquinidine, and was first definitely obtained by Heidelberger and Jacobs.[4] It forms glistening, cream-tinted, hexagonal plates, m.p. 195°, $[\alpha]_D^{19 \cdot 5°} + 253 \cdot 4°$ in alcohol ($c = 1 \cdot 42$). The hydrochloride, $B.HCl.H_2O$, forms prismatic needles, m.p. 231°–233° (*dry*), $[\alpha]_D^{24°} + 194 \cdot 2°$ ($c = 0 \cdot 62$ in water); the dihydrobromide, B.2HBr, pale yellow plates, m.p. above 275°; the hydriodide, $B.HI.H_2O$, pink rhombic plates, m.p. 209°–212° (*dry*). The ethyl ether (ethylhydrocupreidine), $C_{19}H_{23}ON_2.OC_2H_5$, forms slender needles, m.p. 197·5°–198°, $[\alpha]_D + 212 \cdot 8°$ ($c = 1 \cdot 008$ in alcohol), and yields a hydrochloride, $B.HCl. 4H_2O$, flat needles or narrow plates, m.p. 258°–260° (*dry*), $[\alpha]_D^{22} + 183 \cdot 3$ ($c = 0 \cdot 592$ in water).

Constitution of the Chief Cinchona Alkaloids

The four alkaloids, quinine, quinidine, cinchonine and cinchonidine, form two pairs of isomerides, of which each member of the first pair differs from each member of the second by the residue of one methoxyl group, $-CH_2O$. Further, the members of each pair yield for the most part the same products under the action of various reagents, and the products furnished by the two pairs form parallel

[1] Heidelberger and Jacobs, *Journ. Amer. Chem. Soc.* 1922, **44,** 1091.

[2] Giemsa and Halberkann, *Berichte*, 1918, **51,** 1325.

[3] This and the other melting-points recorded in this paragraph are final melting-points after other changes, intumescence, blackening, etc., have taken place; *see* ref. [1].

[4] *Journ. Amer. Chem. Soc.* 1919, **41,** 817. *Cf.* Forst and Böhringer, *Berichte,* 1882, **15,** 1656.

series differing constantly by the residue of a methoxyl group, —CH_2O.

The relationship of cupreine to quinine is established by the fact that it differs from quinine by CH_2, contains a phenolic hydroxyl group, which is not present in quinine, and on methylation yields quinine, cupreine methyl ether. Quinine does not, however, yield cupreine when heated with halogen acids, but apoquinine (p. 138), which is also formed by the action of such acids on cupreine itself. Hydrocinchonine (cinchotine) and hydrocinchonidine (cinchonamidine) have the composition of cinchonine dihydrides, hydroquinine and hydroquinidine are similarly related to quinine, whilst quinamine and conquinamine have the composition of cupreine dihydrides. Among the other cinchona alkaloids, if regard is had merely to empirical composition, relationships to the chief alkaloids of the series can be traced, but there is at present no experimental evidence to justify the view that close relationship exists.

The two alkaloids which have been most completely investigated are quinine and cinchonine. The fission products of both fall into two classes, viz., derivatives of quinoline, and derivatives of a second heterocyclic ring system, formerly referred to as the " second half " of the molecule, but for which the term quinuclidine was coined by Königs. The decomposition products of this " second half " are distinguished by the occurrence in their names of " loipon " (from *loipos*, a residue) or the prefix " mero " (from *meros*, a part).

OXIDATION OF CINCHONINE AND QUININE. This oxidation proceeds in two well-marked stages. In the first the molecular structure is preserved, and changes occur in side or connecting chains only, whilst in the second, fission also takes place, and the characteristic products of the two portions of the nuclei already referred to appear. Both alkaloids contain an unsaturated side-chain, —$CH : CH_2$, and it is this which is first attacked by oxidising agents. Thus cinchonine in acid solution with the calculated quantity of permanganate (2·5 per cent. by weight) yields formic acid and cinchotenine, whilst quinine under similar conditions yields formic acid and quitenine, a reaction which may be illustrated thus : $B—CH : CH_2 + 2O_2 = B.COOH + H.COOH$, where B represents either the cinchonine or quinine residue to which the vinyl group is attached as a side-chain.

Teekles [1] has shown recently that the acyl derivatives of quinine and cinchonine on exposure to ozone form ozonides, which, on

treatment with water, liberate formaldehyde and produce the aldehydes, quininal and cinchoninal, presumably corresponding to quitenine and cinchotenine.

Cinchotenine, $C_{18}H_{20}O_3N_2$, crystallises with $3H_2O$ in needles or leaflets, m.p. 197°, $[\alpha]_D + 135\cdot48°$, and is soluble in water, dilute acids, or alkalis. The base contains two tertiary nitrogen atoms, yields a monoacetyl and a monobenzoyl derivative, and forms salts with acids ; the aurichloride, $(B.2HCl).AuCl_3$, occurs in yellow needles, and the platinichloride, $B.2HCl.PtCl_4$, in orange-coloured prisms. It is also a carboxylic acid and gives an ethyl ester crystallising in minute needles, m.p. 210·5°.[1]

The isomeric substance, *cinchotenidine*,[2] similarly obtained from cinchonidine or homocinchonidine, crystallises in needles, m.p. 256°, $[\alpha]_D - 201\cdot4°$, and, like cinchotenine, gives by further oxidation cinchoninic and cincholoiponic acids.

Quitenine, $C_{19}H_{22}O_4N_2$, the corresponding quinine product,[3] forms rhombic prisms with $4H_2O$ from alcohol, m.p. 286° (*decomp.*), 228° (*dry*), $[\alpha]_D - 142\cdot7°$, slightly soluble in boiling water, insoluble in ether. It gives the thalleioquin reaction, is fluorescent in alcohol or dilute sulphuric acid, and forms salts with acids ; the platinichloride, $B.2HCl.PtCl_4.3H_2O$, crystallises in yellow leaflets. The base gives an ethyl ester and also monoacyl derivatives. Hydriodic acid converts it into quitenol, $C_{18}H_{20}O_4N_2$, and methyl iodide.

The isomeride *quitenidine*, similarly produced by the oxidation of quinidine,[4] crystallises in prisms, m.p. 246°, and, like quitenine, gives quininic and cincholoiponic acids by further oxidation.

When chromic acid is substituted for permanganate the vinyl group remains unattacked, and the two alkaloids each lose two hydrogen atoms forming the ketones cinchoninone and quininone respectively. This reaction implies the conversion of a secondary alcohol group into a carbonyl group, and since cinchonidine also yields cinchoninone, and quinidine, quininone, this secondary alcohol group must play an important part in differentiating the members of the two pairs from each other.

Cinchoninone, $C_{19}H_{20}ON_2$, produced by the oxidation of either cinchonine[5] or cinchonidine[6] by chromic acid in presence of sul-

[1] Hesse, *Annalen*, 1875, **176**, 232 ; Skraup, *ibid.* 1879, **197**, 381.
[2] Skraup and Vortmann, *ibid.* p. 235 ; Hesse, *Berichte*, 1881, **14**, 1892.
[3] Kerner, *Zeit. Chem.* 1869, p. 593 ; Skraup, *Annalen*, 1879, **199**, 348.
[4] Forst and Böhringer, *Berichte*, 1882, **15**, 1659.
[5] Rabe, *ibid.* 1907, **40**, 3281, 3655.
[6] *Annalen*, 1909, **364**, 330.

phuric acid forms pale yellow prisms, m.p. 126°–127°, $[\alpha]_D + 71°$
to $+ 76°$, is sparingly soluble in light petroleum, easily in ether or
chloroform, and insoluble in water. The hydrochloride forms
minute colourless needles, m.p. 245°–247°, $[\alpha]_D + 175·9°$. By
further oxidation with chromic acid, cinchoninone yields cinchoninic
acid and meroquinenine.

Quininone, $C_{20}H_{22}ON_2$, similarly obtained from either quinine [1]
or quinidine, forms colourless or pale yellow needles or leaflets,
m.p. 101°–108°, $[\alpha]_D^{23} + 73·8°$, has about the same solubilities as
cinchoninone, and yields a hygroscopic crystalline hydrochloride,
m.p. 210°–212°, $[\alpha]_D^{14} + 58·7°$.

When cinchonine and quinine are oxidised energetically by
chromic acid, instead of these intermediate ketones, the fission
products of the two nuclei are obtained. The following scheme
illustrates roughly the relationships of these products to the parent
alkaloids. Cinchonidine and quinidine yield respectively the same
products as cinchonine and quinine.

Cinchonine, $C_{19}H_{22}ON_2$

By chromic acid   *By permanganate*

Cinchoninone, $C_{19}H_{20}ON_2$ (1)

By chromic acid $\longrightarrow$ *Cinchotenine*, $C_{18}H_{20}O_3N_2$ (2)

Cinchoninic acid, $C_{10}H_7O_2N$ (3)   Meroquinenine, $C_9H_{15}O_2N$

Cincholoiponic acid, $C_8H_{13}O_4N$

Loiponic acid, $C_7H_{11}O_4N$
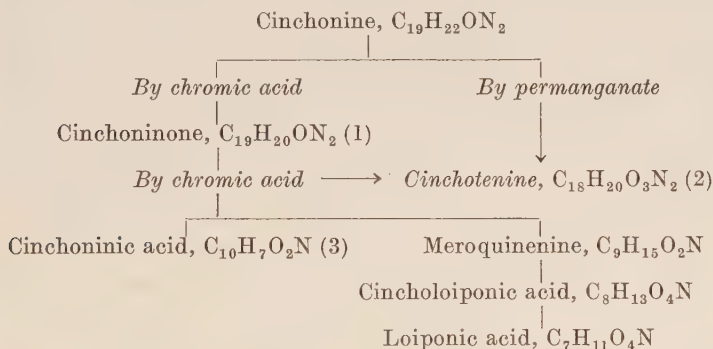
Quinine gives in place of (1) quininone, $C_{20}H_{22}O_2N_2$; in place of
(2) quitenine, $C_{19}H_{22}O_4N_2$; and, instead of (3) quininic acid,
$C_{11}H_9O_3N$, the other products being the same.

The simplest proximate products of the oxidation of the four
alkaloids, therefore, are:

Cinchonine or *cinchonidine*   *Cinchoninic acid* $\Big\}$ and Loiponic acid
                         $C_{10}H_7O_2N$
Quinine or *quinidine*   *Quininic acid* $\Big\{$ $C_7H_{11}O_4N$
                         $C_{11}H_9O_3N$
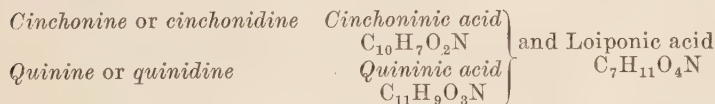
Cinchoninic and quininic acids are well-known quinoline deriva-
tives, viz., quinoline-4-carboxylic and 6-methoxyquinoline-4-carb-
oxylic acids respectively.

[1] *Annalen,* 1909, **364,** 330.

These results indicate that quinine and quinidine differ in structure from cinchonine and cinchonidine in containing a methoxyl group in position 6 on a quinoline nucleus. The identity of the other oxidation products, meroquinenine, cincholoiponic and loiponic acids, in all four cases suggests that the " second half " of the molecule has the same structure in all four alkaloids. Further, this " second half " must be joined to the quinoline nucleus in the *para*-position (carbon atom 4) to the nitrogen atom.

Meroquinenine, $C_9H_{15}O_2N$, formed by the *oxidation* of all four alkaloids and of cinchoninone, and by the *hydrolysis* of quinenine or cinchenine (p. 154), crystallises from methyl alcohol in needles, m.p. 223°–224° (*decomp.*), $[\alpha]_D + 27\cdot5°$ in water. It gives a nitrosamine and a monoacetyl derivative, and is, therefore, a secondary base, whilst it undergoes esterification with ethyl and methyl alcohols, forming the respective esters ; the ethyl ester hydrochloride has m.p. 165°. When oxidised by chromic acid it yields formic and cincholoiponic acids. On reduction with zinc dust and hydriodic acid, it adds on two atoms of hydrogen forming *cincholoipon*, $C_9H_{17}O_2N$, and when heated with hydrochloric acid at 250°–260° gives 3-ethyl-4-methylpyridine (β-collidine).

Cincholoiponic acid, $C_8H_{13}O_4N \cdot H_2O$, results from oxidation of cinchotenine, cinchotenidine, quitenine, quitenidine, meroquinenine, or cincholoipon, and according to Skraup, is also formed directly by the oxidation of cinchonine, cinchonidine, quinine or quinidine. It crystallises from water in prisms, m.p. 126° or 221°–222° (*dry*), is insoluble in alcohol or ether, soluble in water, and dextrorotatory. It furnishes a nitrosamine, a monoacetyl derivative and a diethyl ester (needles, m.p. 181°). On oxidation with permanganate, it produces loiponic acid, $C_7H_{11}O_4N$, and when heated with sulphuric acid 4-methylpyridine and carbon dioxide. Racemic α- and β-cincholoiponic acids were prepared synthetically by Wohl and Losanitsch,[1] and were resolved into their components by Wohl and Maag[2] by crystallisation of the brucine salts. Of these, β-*d*-cincholoiponic acid proved to be identical with the acid obtained from cinchonine.

Loiponic acid, $C_7H_{11}O_4N$, obtained in small quantity by Skraup[3] by oxidising cincholoiponic acid with cold permanganate, forms irregular prisms, m.p. 259° (*decomp.*), from hot water. It behaves

[1] *Berichte*, 1907, **40**, 4698.
[2] *Ibid.* 1909, **42**, 627.
[3] *Monats*, 1896, **17**, 377.

as a dibasic acid, furnishing a diethyl ester, and with acetic anhydride
gives acetylloiponic acid anhydride, m.p. 161°. Königs [1] first
pointed out the isomerism of loiponic acid with hexahydrocincho-
meronic acid (piperidine-3 : 4-dicarboxylic acid). The latter acid
was found to be a mixture of the *cis* and *trans* forms, and by treat-
ment with potash was converted wholly into the more stable of these
forms. Loiponic acid by treatment with potash is also changed
into this stable form, and so must be regarded as a labile modifica-
tion of hexahydrocinchomeronic acid. From the facts recorded
above, it is clear that the oxidation products of the " second half " of
the four alkaloids must be represented by the following formulæ : [2]

$CH.CH_2.COOH$

CH_2 — $CH.CH_2.CH_3$

CH_2 — CH_2

NH

Cincholoipon

$CH.CH_2.COOH$

CH_2 — $CH.CH : CH_2$

CH_2 — CH_2

NH

Meroquinenine

$CH.CH_2.COOH$

CH_2 — $CH.COOH$

CH_2 — CH_2

NH

Cincholoiponic acid

$CH.COOH$

H_2C — $CH.COOH$

H_2C — CH_2

NH

Loiponic acid
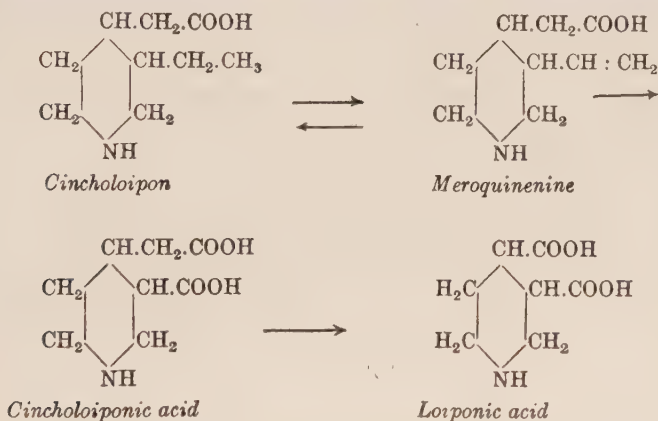
Action of Phosphorus Pentachloride. The oxygen atom in
cinchonine and cinchonidine and the second oxygen atom in quinine
and quinidine are present as alcoholic hydroxyls, since all four
alkaloids yield monoacyl derivatives with acid anhydrides or
chlorides, are not soluble in alkalis, and on gentle oxidation lose two
atoms of hydrogen forming ketones (p. 150). When acted upon by
phosphorus pentachloride, this hydroxyl group is replaced by an
atom of chlorine forming cinchoninechloride, $C_{19}H_{21}N_2Cl$ (needles,
$[\alpha]_D^{13} + 56°$, m.p. 72°), cinchonidinechloride ($[\alpha]_D^{13} + 78°$ m.p. 108°–
109°), quininechloride, $C_{20}H_{23}ON_2Cl$ (minute needles, m.p. 151°,
$[\alpha]_D^{15} + 60°$, gives the thalleioquin reaction), and quinidinechloride
(crystals, $[\alpha]_D^{15} + 35°$, m.p. 131°–132°), respectively. [3]

[1] *Berichte*, 1897, **30**, 1326.
[2] *Loc. cit.* and Königs, *Berichte*, 1902, **35**, 1357. *Cf.* Rabe and
Pasternack, *ibid.* 1916, **49**, 2753.
[3] Comstock and Königs, *Berichte*, 1880, **13**, 286 ; 1884, **17**, 1986 ;
1885, **18**, 1229, 2379. *Cf.* Rabe, *Annalen*, 1910, **373**, 85.

Action of Alcoholic Potash on the " Chlorides." When cinchonine- or cinchonidine-chloride is heated with alcoholic potash a molecule of hydrogen chloride is split off with the formation of CINCHENINE, $C_{19}H_{20}N_2$, leaflets, m.p. 123°–125°. Similarly quinine—or quinidine—chloride is converted into QUINENINE, $C_{20}H_{22}ON_2$, crystallising in trimetric prisms, m.p. 81°–82°, and giving the thalleioquin reaction. When heated with phosphoric acid at 175°, cinchenine and quinenine undergo hydrolysis according to the following equations :

$$C_{19}H_{20}N_2 \quad + \quad 2H_2O \quad = \quad C_9H_{15}O_2N \quad + \quad C_{10}H_9N$$

Cinchenine   *Meroquinenine*   *Lepidine* (*4-methylquinoline*)

$$C_{20}H_{22}ON_2 \quad + \quad 2H_2O \quad = \quad C_9H_{15}O_2N \quad + \quad C_{10}H_8N(OCH_3)$$

Quinenine   *Meroquinenine*   *6-Methoxylepidine*
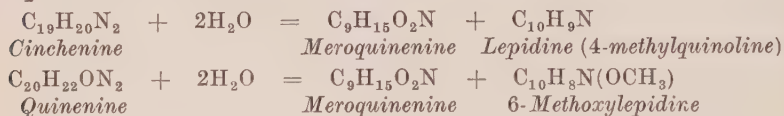
These hydrolyses afford further evidence of the existence in the four alkaloids of a quinoline nucleus and of a second ring system containing a nitrogen atom, whilst the production of 6-methoxy-lepidine from quinine and quinidine, and of lepidine from cinchonine and cinchonidine, supports the view that the two former have the composition, but not necessarily the physical structure, of 6-methoxycinchonines. The formulæ of the two alkaloids may, therefore, be extended thus : *Cinchonine*, $C_9H_6N.C_{10}H_{15}(OH)N$; *Quinine*, $CH_3O.C_9H_5N.C_{10}H_{15}(OH)N$, the complex, $C_{10}H_{15}(OH)N$, being the origin of meroquinenine (1) in the hydrolyses of cinchenine and quinenine, and (2) in the oxidation of the parent alkaloids.

Structure of the " Second Half." When cinchenine is heated with haloid acids at 180°, it undergoes a remarkable decomposition, taking up 1 mol. H_2O, and then losing 1 mol. of ammonia, producing a new base, APOCINCHENINE, $C_{19}H_{19}ON$, needles, m.p. 209°–210°. Similarly quinenine heated with hydrobromic acid at 190° decomposes with the production of methyl bromide, ammonia and APO-QUINENINE, $C_{19}H_{19}O_2N$. The latter, when fused with zinc ammonium chloride, gives aminoapocinchenine, which by diazotisation and treatment with alcohol and copper powder gives apocinchenine, identical with that obtained from cinchenine.[1] Apoquinenine, must, therefore, be a hydroxyapocinchenine.

Apocinchenine furnishes cinchoninic acid on oxidation so that the changes involved in its formation from cinchonine and quinine must have taken place in the " second half." Comstock and Königs have also shown that it behaves as a phenol, giving ethers when

[1] Königs, *J. prakt. Chem.* 1900, [ii], **61**, 41.

treated with alkyl haloids in presence of alkali. It may, therefore, be assumed provisionally that apocinchenine contains, in addition to the quinoline complex, a benzene ring, attached to the former in the *para* position with respect to the nitrogen atom : its formula may, therefore, be written, $C_9H_6N.C_6H_2(OH):C_4H_{10}$. The nature of the group C_4H_{10} was arrived at in the following manner : Apocinchenine ethyl ether, m.p. 70°, is oxidised by acid permanganate to *apocincheninic acid ethyl ether*, $C_{20}H_{19}O_3N$; the latter, when heated with hydrobromic acid, undergoes hydrolysis, and at the same time loses carbon dioxide and forms *homoapocinchenine*,[1] $C_{17}H_{15}ON$.

$$C_6H_2\!\!\begin{array}{c}{}^{\diagup C_4H_{10}}\\{}_{\diagdown OH}\end{array} \qquad C_6H_2\!\!\begin{array}{c}{}^{\diagup C_4H_{10}}\\{}_{\diagdown OC_2H_5}\end{array} \qquad C_6H_2\!\!\begin{array}{c}{}^{\diagup C_2H_5}\\{}^{-COOH}\\{}_{\diagdown OC_2H_5}\end{array} \qquad C_6H_3\!\!\begin{array}{c}{}^{\diagup C_2H_5}\\{}_{\diagdown OH}\end{array}$$
$$|\qquad\qquad |\qquad\qquad |\qquad\qquad |$$
$$C_9H_6N \qquad\quad C_9H_6N \qquad\quad C_9H_6N \qquad\quad C_9H_6N$$

Apocinchenine   *Apocinchenine*   *Apocincheninic acid*   *Homoapocin-*
             ethyl ether   *ethyl ether*   *chenine*
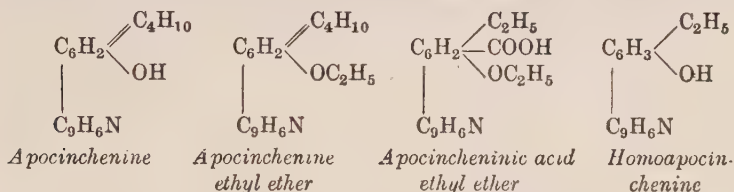
The latter, by a similar series of reactions, is converted into homoapocincheninic acid ethyl ether ; the silver salt of this on heating loses carbon dioxide, giving quinolylphenetole, which, with hydrobromic acid undergoes hydrolysis, forming a quinolylphenol, identical with o-hydroxy-4-phenylquinoline prepared synthetically.

$$C_6H_3\!\!\begin{array}{c}{}^{\diagup C_2H_5}\\{}_{\diagdown OC_2H_5}\end{array} \qquad C_6H_3\!\!\begin{array}{c}{}^{\diagup COOH}\\{}_{\diagdown OC_2H_5}\end{array} \qquad C_6H_3\!\!\begin{array}{c}{}^{\diagup H}\\{}_{\diagdown OC_2H_5}\end{array} \qquad C_6H_4OH$$
$$|\qquad\qquad\qquad |\qquad\qquad\qquad |\qquad\qquad\quad |$$
$$C_9H_6N \qquad\qquad C_9H_6N \qquad\qquad C_9H_6N \qquad\qquad C_9H_6N$$

Homoapocinchenine   *Homoapocincheninic*   *Quinolylphenetole*   *Quinolyl-*
      ethyl ether   *acid ethyl ether*   *phenol*
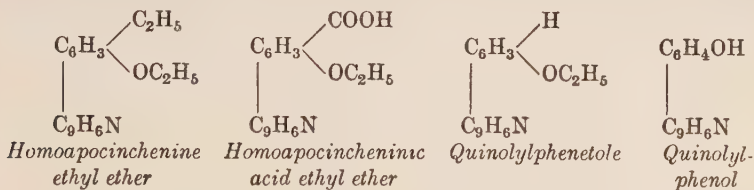
In apocinchenine the hydroxyl group must, therefore, be in the *ortho* position relative to the point of attachment of the benzene ring to the quinoline nucleus. The relative positions of the two ethyl groups are determined by the fact that apocincheninic acid ethyl ether on oxidation with manganese dioxide and sulphuric acid gives the lactone of hydroxyapocincheninic acid ethyl ether (I), which, on oxidation by sodium hypobromite, yields quinolylphenetoledicarboxylic acid (II). The latter must have its two carboxyl groups :

$$C_9H_6N.C_6H_2(OC_2H_5)\!\!\begin{array}{c}{}^{\diagup CO-\!\!\!\!\!-}\\{}_{\diagdown CHMe-}\end{array}\!\!\!O \;\rightarrow\; C_9H_6N\;C_6H_2(OC_2H_5):(COOH)_2$$

                      I   II
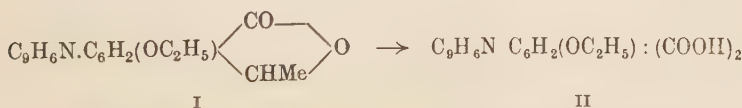
Comstock and Königs, *Berichte,* 1885, **18**, 2384 ; 1887, **20**, 2683.

in the *ortho* position to each other, since it readily yields an anhydride and, on fusion with resorcinol, gives a fluorescein. Apocinchenine must, therefore, be represented by one of the following formulæ, of which II is the most probable, since it best explains the formation of nitroapocinchenine by the action of nitrous acid,[1] position 5 (para to the HO— group) being then free for the entry of the —NO_2 group :

I. $C_9H_6N.C_6H_2Et_2.OH$ (C_9H_6N : Et : Et : OH $= 1 : 4 : 5 : 2$)
II. $C_9H_6N.C_6H_2Et_2.OH$ (C_9H_6N : Et : Et : OH $= 1 : 3 : 4 : 2$)
III. $C_9H_6N.C_6H_2Et_2.OH$ (C_9H_6N : Et : Et : OH $= 1 : 5 : 6 : 2$)

The facility with which the " second half " of the molecule furnishes benzenoid derivatives recalls the similar behaviour of tropine and ecgonine, and several formulæ representing cinchonine and quinine, and their isomerides as containing a quinoline ring attached to a bicyclic ring system similar to that of the tropine group have been proposed.[2] The formula now generally accepted for cinchonine is due mainly to Königs, and has received ample confirmation from recent work, especially of Rabe and his collaborators :

Cinchonine (Königs)
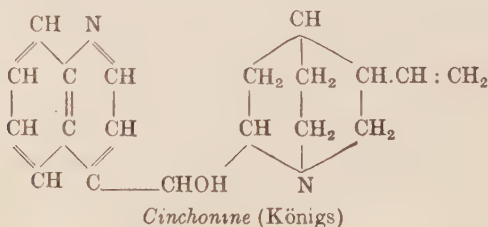
In particular this formula has now been shown to account satisfactorily for the following characteristic reactions of this group of alkaloids. When cinchonine sulphate is heated dry, or with various reagents, or with water alone, it is converted into an isomeride, cinchonicine (cinchotoxine), already referred to (p. 141), which may also be obtained in like manner from cinchonidine. Quinine and quinidine, under similar treatment, give rise to quini-

[1] Königs, *J. prakt. Chem.* 1900, **61**, 1.
[2] Von Miller and Rohde, *Berichte*, 1894, **27**, 1187, 1280 ; 1895, **28**, 1056 ; 1900, **33**, 3214 ; Pictet and Wolffenstein, *Die Pflanzen Alkaloide*, p. 315 ; Königs, *Berichte*, 1899, **32**, 3599 ; 1907, **40**, 2873 ; *Annalen*, 1906, **347**, 143 ; Rohde and Antonaz, *Berichte*, 1907, **40**, 2329 ; and Rabe, *Annalen*, 1906, **350**, 180.

cine (quinotoxine), which has been described already (p. 137), and the reaction also takes place with cupreine and with the dihydrogenated derivatives of all five alkaloids. Cinchonicine and quinicine, unlike their generators, are keto-bases, and contain both a secondary and a tertiary nitrogen atom.

When treated with amyl nitrite they form oximino compounds, which, with phosphorus pentachloride, furnish, in the case of oximinocinchonicine, cinchoninic acid and meroquineninenitrile, and in the case of oximinoquinicine, quininic acid and meroquineninenitrile.[1] Rabe has also shown that cinchonine methiodide and cinchonidine methiodide both yield the same methylcinchonicine (methylcinchotoxine) on treatment with alkali.[2] These reactions are readily explicable from the following formulæ, in which Q represents the quinoline residue $—C_9H_6N$, and the * indicates the point at which oximino substitution takes place[3]:

$$CH_2:CH.CH.CH.CH_2 \quad CH_2:CH.CH. \quad \overset{*}{CH.CH_2.CH_2.CO.Q} \quad CH.CH_2.CN$$

Cinchonine   *Cinchonicine*   *Meroquineninenitrile*
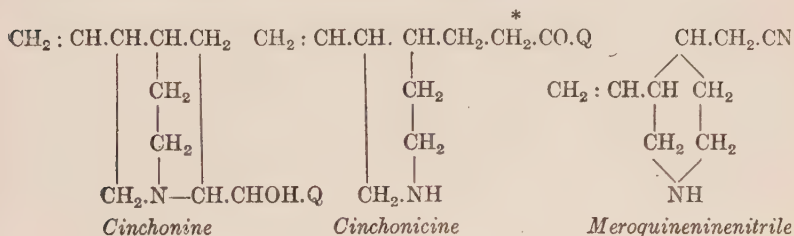
Rabe and his co-workers have also shown that when cinchonine, cinchonidine, quinine, quinidine, or their hydrogenated derivatives are gently oxidised they yield ketones differing by two atoms of hydrogen from the parent alkaloids (*cf.* p. 150). Thus:

Cinchonine and cinchonidine yield cinchoninone, $C_{19}H_{20}ON_2$.

Quinine and quinidine yield quininone, $C_{20}H_{22}O_2N_2$.

Hydrocinchonine yields hydrocinchoninone (cinchotinone), $C_{19}H_{22}ON_2$.

These ketones react with nitrous acid, furnishing oximino derivatives which undergo characteristic decompositions; thus cinchoninone with nitrous acid gives cinchoninic acid and an oxime (β-vinyl-α'-quinuclidoneoxime), $C_9H_{13}N:NOH$, which on hydrolysis by acids yields meroquinenine and hydroxylamine. It must be assumed, therefore, that in the formation of these ketones a secondary carbinol group is converted into a $—CO$ group, so that cinchoninone may be

[1] Rabe and collaborators, *Annalen*, 1906, **350**, 180; 1911, **382**, 365.

[2] *Annalen*, 1909 **365**, 366.

[3] *Cf.* Rohde and Antonaz, *Berichte*, 1907, **40**, 2329; 1909, **42**, 2182.

represented by the following formula where Q represents the quino-
line residue [1] :

$$CH_2 : CH.CH.CH. CH_2$$
$$\begin{array}{cc} & CH_2 \\ & CH_2 \\ CH_2.N & —CH.CO.Q \end{array} \quad + HO.NO \quad$$

Cinchoninone

$$CH_2 : CH.CH.CH. CH_2$$
$$\begin{array}{cc} & CH_2 \\ & CH_2 \\ CH_2.N & —C : NOH \end{array} \quad + Q.COOH$$

β - *Vinyl-α'-quinuclidoneoxime*
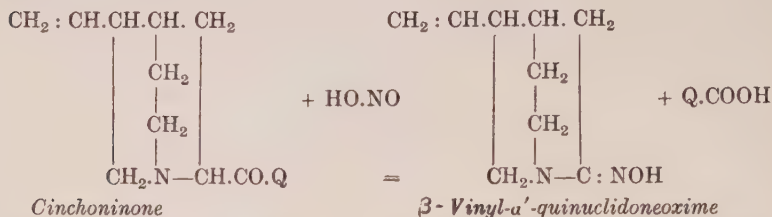
Cinchoninone is also formed by the action of alkali on *N*-bromo-
cinchonicine, and since cinchoninone can be reduced to cinchonine,[1]
it is possible in this way to reconvert cinchonicine into cinchonine
and quinicine into quinine.[2]   On the basis of all these results, Rabe [3]
assigns the following general formula (I) developed from that of
Königs (p. 156) to this group of alkaloids :
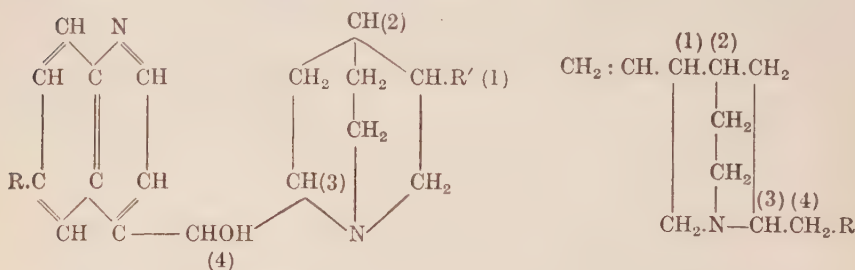
I *Cinchona alkaloids*   II *Deoxy-bases*

In cinchonine and cinchonidine, $R = H . R' = .CH : CH_2$.
In cupreine, $R = .OH . R' = .CH : CH_2$.
In quinine and quinidine, $R = .OCH_3 . R' = .CH : CH_2$.
In the hydro-bases, R' becomes $.CH_2 . CH_3$.
In the alkylcupreines, R becomes $.OAlk$ (homologues of quinine).
In the alkylhydrocupreines and alkylhydrocupreidines, R
    becomes $.OAlk$, and R' becomes $.CH_2 . CH_3$ (homologues of
    dihydroquinine and dihydroquinidine).
In hydroquinine and hydroquinidine, $R = .OCH_3$, $R' =$
    $.CH_2 . CH_3$.

The carbon atoms numbered (1), (2), (3), (4) in the general

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[1] *Berichte*, 1907, **40**, 3655 ; 1908, **41**, 62 ; *Annalen*, 1909, **364**, 330.
[2] Rabe, *Berichte*, 1911, **44**, 2088 ; 1918, **51**, 466 ; *also* p. 165 of this
book.
[3] *Annalen*, 1909, **365**, 353 ; 1910, **373**, 85.

formula, are asymmetric. Since cinchoninone and quininone are both dextrorotatory and both yield β-vinyl-α'-quinuclidineoxime of the same optical activity it follows that cinchonine, cinchonidine, quinine and quinidine, must be optically identical as regards carbon atoms (1) and (2), that the distribution in space is the same about these atoms, and in all four cases is dextrorotatory in total effect. But the deoxy-bases obtained from cinchonine and quinidine and from cinchonidine [1] and quinine are structurally identical, but differ in optical properties, the first pair being dextro- and the second pair lævorotatory. These deoxy-bases have the general formula II, where R is C_9H_6N for cinchonine and cinchonidine, and C_9H_5. (OMe)N for quinine and quinidine and carbon atom (4) is no longer asymmetric.[2] It follows that difference in optical activity in these bases, and, therefore, in the four alkaloids from which they are derived, depends on the arrangement of groups round carbon atom (3), and is different in sign in the two pairs.

In the formation of cinchonicine and quinicine the asymmetry of carbon atoms (3) and (4) disappears (see formula, p. 157), and consequently in this reaction each pair of isomerides gives rise to a single substance, cinchonine and cinchonidine producing cinchonicine and quinine and quinidine yielding quinicine. The keto-bases, cinchoninone and quininone, on the contrary, might be expected to exist each in two pairs, since carbon atom (3) is, according to the formula (p. 158) asymmetric, but it is better represented by the tautomeric grouping : [3]

$$-CO.CH \rightleftharpoons C(OH):\overset{.}{\underset{.}{C}}$$
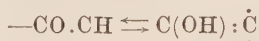
(the evidence for this being that the bases show mutatotation), so that in these keto-bases the asymmetry of carbon atom (3) is not readily observable, but it becomes evident on reduction, especially in the case of dihydrocinchoninone, which on reduction by aluminium in an alcoholic solution of sodium ethoxide yields dihydrocinchonine (cinchotine, $[\alpha]_D + 190°$), dihydrocinchonidine (cinchamidine, $[\alpha]_D - 98°$), and two new alkaloidal secondary alcohols having $[\alpha]_D + 88.5°$ and $48°$ respectively.[4] Using these and the other data

[1] Königs, Berichte, 1896, 29, 372. Cf. Rabe, Annalen, 1910, 373, 85.
[2] In the dihydro-deoxybases $CH_2 : CH$ becomes $-CH_3.CH_2-$. Cf. Freund and Bredenburg, Annalen, 1914, 407, 43.
[3] Rabe and co-workers, Annalen, 1910, 373, 85. Cf. Kaufmann and Huber, Berichte, 1913, 46, 2913.
[4] German Patent 330,813 (Chem. Soc. Abstr. 1921 [i], 355). Cf. Kaufmann and Huber, loc. cit.

referred to above, King,[1] in a useful discussion of the whole subject of the contribution of each of the asymmetric carbons to the optical rotation of the principal cinchona alkaloids, suggests that the values are made up as follows :

	Asymmetric Carbon Atoms.			
	1	2	3	4
Cinchonine and hydrocinchonine	+	+	+	+
Cinchonidine and hydrocinchonidine	+	+	−	−
Quinine and hydroquinine	+	+	−	−
Quinidine and hydroquinine	+	+	+	+

Rabe [2] has pointed out that of the thirty-two possible stereo-isomerides of cinchonine, which might be expected to arise from the presence of four asymmetric carbons with an asymmetric tervalent nitrogen in the molecule, only sixteen are actually capable of existence owing to the fact that the nitrogen and one of the carbon atoms (No. 3) constitute the terminals of the bridge in the bridged piperidine (quinuclidine) ring.

Nomenclature in the Cinchona Series

To the bridged piperidine ring, which may be regarded as the parent structure of the " second half " of the cinchona alkaloids, Königs [3] has applied the name quinuclidine, and this has come into general use (see formula p. 161). In 1917 when the multiplication of compounds conforming to a few general types, and all derived from the cinchona alkaloids began to be embarrassing, various attempts were made by systematists to improve the nomenclature, and Kaufmann, Rothlin and Brunnschweiler [4] adopted Pasteur's original name of quinicine for quinotoxine, and so substituted the termination " icine " for " toxine," whence dihydrocinchotoxine has become dihydrocinchonicine, and also cinchoticine from cincho-tine (dihydrocinchonine). This has been adopted in part, but the net result so far has been to increase the synonomy, as in the example quoted above, and the introduction of cupreicine for cupreinotoxine. The whole group of keto-bases concerned is generally known as the " quinatoxines," a name which has also been applied to certain

[1] *Trans. Chem. Soc.* 1922, **121**, 2578.
[2] *Berichte*, 1922, **55**, 522.
[3] *Ibid.* 1904, **37**, 3244.
[4] *Ibid.* 1916, **49**, 2299.

synthetic 4-quinolyl ketones,[1] an extension to which Rabe objects.[2] The difference may be represented simply thus:

$$CH\Big\langle{\overset{\displaystyle CH_2.CH_2}{\underset{\displaystyle CH_2.CH_2}{CH_2.CH_2}}}\Big\rangle N \qquad CH\Big\langle{\overset{\displaystyle CH_2—CH_2—CO.Q}{\underset{\displaystyle CH_2—CH_2}{CH_2—CH_2—NH}}} \qquad NHMe.(CH_2)_n.CO.Q$$

Quinuclidine   *Typical quinatoxine*   *Aliphatic quinatoxine*
(Königs)   (Rabe)   (Ruzicka)
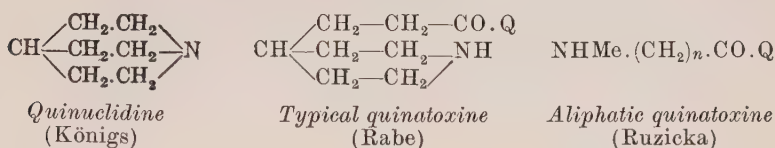
As the basis of a better system of nomenclature, Rabe[2] has suggested the names ruban for 4'-quinolylquinuclidine, which may be regarded as the parent substance of the natural alkaloids, and rubatoxan for that of the quinatoxins:
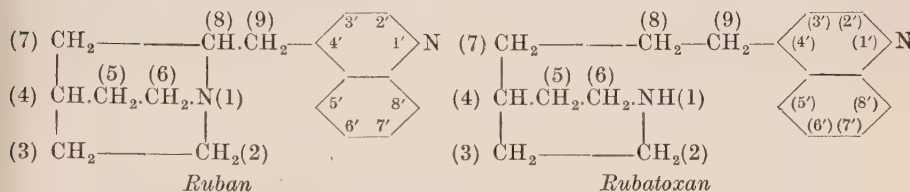
Ruban   *Rubatoxan*

On this system cinchonine becomes 3-vinyl-ruban-9-ol, cinchoninone is 3-vinyl-ruban-9-one, cinchonicine 3-vinyl-rubatoxan-9-one, whilst quinine is 6'-methoxy-3-vinyl-ruban-9-ol, and quinicine is 6'-methoxy-3-vinyl-rubatoxan-9-one. Rabe would confine the term "quinatoxine" to 4'-quinolyl ketones, which are derivatives of rubatoxan-9-one.

An innovation, which seems unnecessary, is Heidelberger and Jacobs[3] suggestion that the deoxy-bases should be renamed by the use of the suffix -ane, deoxyquinine becoming quinane. This, like other recent proposals, is not in harmony with the useful Anglo-American convention that the names of basic substances should end in -ine.

Synthetic Work on Cinchona Alkaloids

Though a complete synthesis of a cinchona alkaloid has not yet been effected, much work in this direction has been carried out. Further, many efforts have been made to prepare in the laboratory simpler substances containing the groups with which pharmacologists have from time to time associated the characteristic pharmacological

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[1] *See e.g.*, Ruzicka, *Helv. Chim. Acta*, 1921, **4**, 486.
[2] *Berichte*, 1922, **55**, 522.
[3] *Journ. Amer. Chem. Soc.* 1920, **42**, 1489.

action of quinine and its allies.   A third type of synthetic work to which much attention has been given in recent years is that of varying the side-chains of the quinine molecule in the hope of producing substances of enhanced therapeutical value, and which may be called "modified cinchona alkaloids." The results of investigations in these three directions are very voluminous, and only an outline of them can be given here.

Syntheses of Cinchoninic and Quininic Acids. It has already been pointed out that quinine, quinidine, cinchonine and cinchonidine all break down on oxidation into two types of products, derivatives of (1) quinoline, and (2) quinuclidine. The former are represented by cinchoninic acid and 6-methoxycinchoninic acid (quininic acid). A number of syntheses of these two acids have been effected, and recent work has been devoted chiefly to improving the yield. The first synthesis of quininic acid is due to Pictet and Misner,[1] who obtained it by the method used by Beyer for 4-methylquinoline,[2] by condensing *p*-anisidine with ethyl pyruvate and formaldehyde, but the yield was only about 5 per cent. of that theoretically possible. A better method is that due to Kaufmann and Peyer,[3] who found that 6-methoxyquinoline methosulphate reacts with potassium cyanide to give 4-cyano-6-methoxy-1-methyl-1 : 4-dihydroquinoline (I), which with iodine yields 4-cyano-6-methoxyquinoline methiodide (II). The latter on distillation under reduced pressure gives quinononitrile, which on hydrolysis by acids or alkalis in presence of hydrogen peroxide, yields quininic acid (III). Cinchoninic acid is obtained by the analogous process applied to quinoline methosulphate.

$$\text{MeO.C}_6\text{H}_3 \Big\langle \begin{array}{c} \text{CH(CN).CH} \\ \| \\ \text{NHMe--CH} \end{array} \qquad \text{MeO.C}_6\text{H}_3 \Big\langle \begin{array}{c} \text{C(CN) : CH} \\ | \\ \text{NMeI=CH} \end{array} \qquad \text{MeO.C}_6\text{H}_3 \Big\langle \begin{array}{c} \text{C(COOH) : CH} \\ | \\ \text{N=====CH} \end{array}$$

$$\qquad\qquad \text{I} \qquad\qquad\qquad\qquad\qquad \text{II} \qquad\qquad\qquad\qquad\qquad \text{III}$$
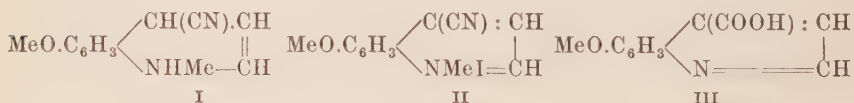
The yields are stated to be almost quantitative for 6-methoxyquinoline.

Synthesis of Quinuclidine and its Derivatives. Quinuclidine itself (or a near derivative of it) is not obtained by the direct decomposition of the chief cinchona alkaloids, but this part of the nucleus

[1] *Berichte*, 1912, **45**, 1800.

[2] *J. prakt. Chem.* 1886, **33**, 393.

[3] *Berichte*, 1912, **45**, 1885.   *Cf.* Kaufmann and Widmer, *ibid.* 1911, **44**, 2052, 2058 ; and previous and later papers in the same series : 1909, **42**, 1999, 3776 ; 1918, **51**, 116 ; *cf. also* Halberkann, *ibid.* 1922, **54**, 3079, 3090.

is represented by loiponic and cincholoiponic acids, meroquinenine and cincholoipon for which the following formulæ are now accepted :

CH.COOH
H₂C   CH.COOH
H₂C   CH₂
NH
Loiponic acid

CH.CH₂.COOH
CH₂   CH.COOH
CH₂   CH₂
NH
Cincholoiponic acid
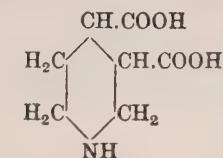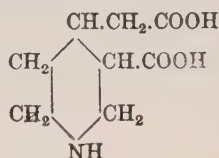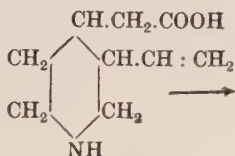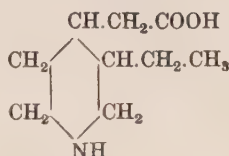
CH.CH₂.COOH
CH₂   CH.CH : CH₂
CH₂   CH₂
NH
Meroquinenine
⟶
CH.CH₂.COOH
CH₂   CH.CH₂.CH₃
CH₂   CH₂
NH
Cincholoipon

These can all be regarded as derivatives of 3-ethyl-4-methyl-pyridine (β-collidine), obtained by de Coninck [1] by distilling cin-chonine with alkalis, and later by Königs [2] from meroquinenine. This was synthesised by Ruzicka and Fornasir [3] in 1919, by a method depending on the preparation of 2 : 6-dihydroxy-3-ethyl-4-methyl-pyridine by the general process used by Rogerson and Thorpe,[4] conversion of this into 2 : 6-dichloro-β-collidine by phosphoryl chloride and removal of the chlorine atoms by means of hydriodic acid.[5] β-Collidine had already been converted into 3-ethylquinu-clidine by Königs [6] by prolonged heating in a closed vessel with formaldehyde and acetic acid when condensation to 4-methylol-β-collidine took place. The latter was reduced to the corresponding hexahydro derivative (I) by means of sodium and alcohol, and this by prolonged treatment with hydriodic acid and phosphorus yielded 3-ethyl-4-iodoethylhexahydropyridine (II), which on careful addition of ice-cold caustic soda solution and agitation with ether underwent internal condensation with the formation of 3-ethylquinuclidine (III) (b.p. 190°–192°/720 mm., B.HCl, m.p. 208°–211°, picrate, m.p. 153°–

[1] *Annales de Chimie*, 1882 [v], **27,** 469.
[2] *Berichte*, 1894, **27,** 1502.
[3] *Helv. Chim. Acta.* 1919, **2,** 338.
[4] *Trans. Chem. Soc.* 1905, **87,** 1685.
[5] For a synthesis from homonicotinic acid, *see* Rabe and Jantzen, *ibid.* 1921, **54,** 925.
[6] *Berichte*, 1904, **37,** 3245.   *Cf. ibid.* 1902, 35, 1355 (with Bernhart) ; 1905, **38,** 3049.

154°), which by comparison with the general formula for cinchona

```
 CH.CH₂.CH₂.OH    CH.CH₂.CH₂.I     CH            CH   CH
 /\               /\             /  |          //\    |
CH₂ CHEt         CH₂ CHEt      CH₂ CH₂ CH.Et  CH  C  CH₂ CH₂
 |  |             |  |          |   |   |      |  ||   |   |
CH₂ CH₂          CH₂ CH₂       CH₂ CH₂ CH₂    CH  C  CH₂ CH₂
 \/               \/             \   |   /     \\/    |
 NH               NH               N          CH   N
  I                II              III          IV
```
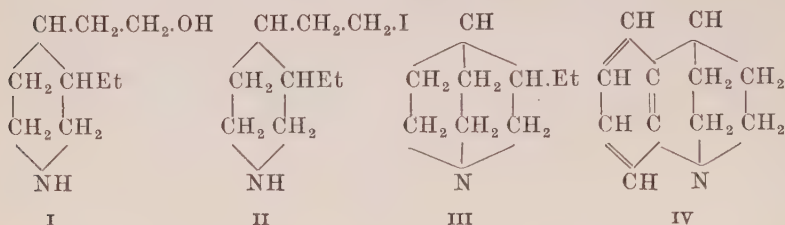
alkaloids (p. 158), is seen to be the " second half " of the dihydro-alkaloids. Cincholoipon it will be seen is the carboxylic acid corresponding to the alkine 4-methylol-β-collidine (I), and Königs and Bernhart [1] showed that cincholoipon ethyl ester on reduction, first with sodium in alcohol and then with hydriodic acid and phosphorus, also yielded 3-ethylquinuclidine, which, unlike that prepared from β-collidine itself, was optically active. Quinuclidine itself was prepared by a somewhat similar process by Löffler and Stietzel [2] from 4-methylpyridine (γ-picoline) and more recently by Meisenheimer and his collaborators [3] (whose data for quinuclidine differ considerably from those of Löffler and Stietzel) who have also prepared the quinoline analogue of quinuclidine, viz., benzoquinuclidine (IV).

From the foregoing, it will be seen that complete syntheses have now been effected of the two halves of the molecular structure characteristic of the chief cinchona alkaloids, but there remains to be achieved the synthesis of d- and l-homocincholoipons and of d- and l-homomeroquinenine, which seem to be the most promising forms in which the " second half " can be grafted on to cinchoninic and quininic acids. Königs and Ottmann [4] have prepared r-homocincholoipon by a modification of the general method already described by condensing chloral with β-collidine in presence of zinc chloride and treating the 3-ethyl-4-β-hydroxy-$\gamma\gamma\gamma$-trichloro-n-propyl pyridine so formed with alcoholic potash to produce β-3-ethylpyridyl-4-acrylic acid, which on reduction by sodium in hot amyl alcohol gives homocincholoipon (needles, m.p. 225° (corr), aurichloride leaflets, m.p. 178° (corr)). The yield is small, and the product has

[1] Berichte, 1905, 38, 3057.
[2] Ibid. 1909, 42, 124.
[3] Annalen, 1920, 420, 190.
[4] Berichte, 1921, 54, 1343.

not yet been deracemised.   Meanwhile Rabe and Kindler [1] have found that ethyl N-benzoylhomocincholoipon, prepared from N-benzoyldihydrocinchonicine (N-benzoylcinchoticine) by Kaufmann, Rothlin and Brunnschweiler's method,[2] condenses with ethyl cinchoninate in presence of sodium ethoxide to form the β-ketonic ester :

$$\text{NBz} \Big\langle{}^{\text{CH}_2\text{---CH}_2}_{\text{CH}_2\cdot\text{CHEt}}\Big\rangle \text{CH}\cdot\text{CH}_2\cdot\text{CH(CO}_2\text{Et)}\cdot\text{CO}\cdot\text{C}_9\text{H}_6\text{N,}$$
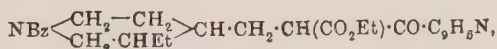
which by hydrolysis with boiling 15 per cent. hydrochloric acid is converted into dihydrocinchonicine.   The latter by the process described below yields dihydrocinchoninone,[3] and this, on reduction with aluminium and sodium hydroxide, furnishes a mixture of dihydrocinchonine and dihydrocinchonidine (*see* p. 159).   By a similar method the same authors have prepared dihydroquinicine using ethyl quininate in place of ethyl cinchoninate,[4] and have so obtained dihydroquinine and dihydroquinidine.   Hence, as Ruzicka and Seidel [5] have pointed out, the synthesis of two of the dihydrogenated cinchona alkaloids is now complete with the exception that synthetic d- and l- forms of homocincholoipon have not yet been prepared.

As cinchonicine and quinicine seem likely to be the intermediates by which complete syntheses of cinchonine and quinine will ultimately be effected, it is interesting to note that Rabe and his collaborators [6] have effected the reconversion of cinchonicine, quinicine, and dihydroquinicine (I) into cinchonine, quinine, and dihydroquinine (IV) respectively, by treating them with sodium hypobromite, forming the N-bromo-derivative (II) (the 8-bromo-derivative may also be used, see p. 168).   The latter is converted by alkali hydroxide into the corresponding quina-ketone (III), which is then reduced to the alkaloid by means of aluminium powder and sodium ethoxide solution.   The changes may be represented thus : where R may be a vinyl- or ethyl-group, and Q is quinolyl or 6-methoxyquinolyl.

[1] *Berichte*, 1918, **51**, 1360.   *Cf.* German Patent 330,945 (*Chem. Soc. Abstr.* 1921 [i], 360); and German Patent 268,830 (*ibid.* 1914 [i], 575).

[2] *Ibid.* 1916, **49**, 2299.   *Cf.* German Patent 313,321 (*Chem. Soc. Abstr.* 1920 [i], 78).

[3] Kaufmann and Huber, *Berichte*, 1913, **46**, 2913.

[4] *Ibid.* 1919, **52**, 1842.

[5] *Helv. Chim. Acta.* 1921, **4**, 482.

[6] *Berichte*, 1911, **44**, 2088 ;   1912, **45**, 2163 ;   1918, **51**, 466.   *Cf.* Kaufmann and Huber, *loc. cit.* (ref. 2).

$$
\begin{array}{ll}
\text{R.CH—CH—CH}_2 & \text{R.CH—CH—CH}_2 \\
\quad\quad | & \quad\quad | \\
\quad\text{CH}_2\quad | & \quad\text{CH}_2\quad | \\
\quad\quad | & \quad\quad | \\
\quad\text{CH}_2\quad | & \quad\text{CH}_2\quad | \\
\quad\quad | & \quad\quad | \\
\text{CH}_2\text{--NH} \;\; \text{CH}_2\text{CO.Q} & \text{CH}_2\text{--NBr} \;\; \text{CH}_2.\text{CO.Q} \\
\qquad\text{I} & \qquad\text{II}
\end{array}
$$

$$
\begin{array}{ll}
\text{R.CH—CH—CH}_2 & \text{R.CH—CH—CH}_2 \\
\quad\quad | & \quad\quad | \\
\quad\text{CH}_2 & \quad\text{CH}_2 \\
\quad\quad | & \quad\quad | \\
\quad\text{CH}_2 & \quad\text{CH}_2 \\
\quad\quad | & \quad\quad | \\
\text{CH}_2\text{—N——CH.CO.Q} & \text{CH}_2\text{—N——CH—CHOH.Q} \\
\qquad\text{III} & \qquad\text{IV}
\end{array}
$$
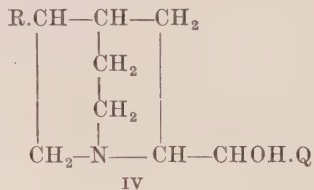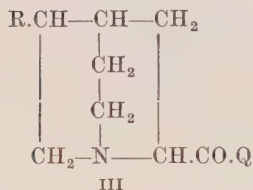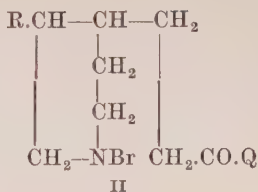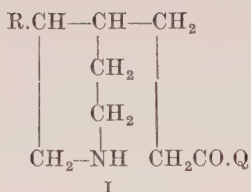
Synthesis of Quinolyl Ketones. The important part played by
the quinolyl ketones typified by quinicine and cinchonicine in the
later stages of the investigation of the molecular structure of
the cinchona alkaloids, and also their value as initial products
for the manufacture of " modified " cinchona alkaloids has led
to the preparation of a number of new substances of this type.
With the idea that the specific action of quinine in malaria is
due to the presence of the —CH(OH).CH.N : group, Kaufmann,
Peyer and Kunkler,[1] prepared from 4-cyanoquinoline by the use
of appropriate Grignard reagents a number of 4-quinolyl alkyl
and aryl ketones, which, on examination pharmacologically by
Warschawski,[2] were shown to possess antipyretic properties, and to
be of relatively low toxicity though they resemble in structure the
poisonous quinicine (quinotoxine) rather than quinine. Kaufmann
then found [2] that 6-alkyloxy-4-quinolyl ketones having methyl or
methylene attached to the carbonyl group reacted with halogens
giving derivatives, which condense with primary amines, and could
then be reduced to the corresponding alcohols. The latter proved
to have the same physiological action as quinine, to be fluorescent,
and to give the thalleioquin reaction. In this way 6-ethoxy-4-
quinolyl methyl ketone was converted into the monobromo deriva-
tive (I) which in the form of the hydrobromide reacted with piperidine
dimethylamine, or diethylamine to form compounds of the type

[1] *Berichte*, 1912, **45**, 3090. Such substances had been prepared
previously, *e.g.*, by Remfry and Decker, *ibid.* 1908, **41**, 1007, by some-
what similar means. *Cf.* also German Patents 268,830, 280,970 (*Chem.
Soc. Abstr.* 1914 [i], 575 ; 1915 [i], 720).
[2] *Berichte*, 1913, **46**, 1823.

represented by formula II (6-ethoxy-4-quinolyl piperidino-methyl

$$CO.CH_2Br \qquad\qquad CO.CH_2.C_5H_{10}N$$

EtO ⟨ ⟩ N   Et.O ⟨ ⟩ N

I   II
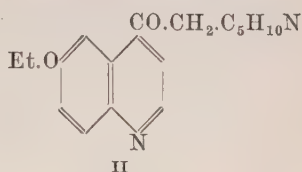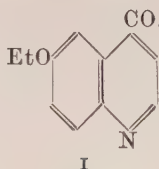
ketone). These on catalytic hydrogenation yielded the corresponding secondary alcohols (*e.g.*, 6-ethoxy-4-β-piperidino-α-hydroxyethylquinoline, III) which have a general resemblance to the typical structure of the cinchona alkaloids IV.

$$CH(OH).CH_2.C_5H_{10}N \qquad CH \quad C.C_{10}H_{15}(OH).N$$

EtO ⟨ ⟩ N

$$CH_3O.C \quad C \quad CH$$
$$CH \quad C. \quad CH$$
$$CH \quad N$$

III   IV   *Quinine*
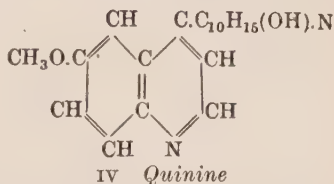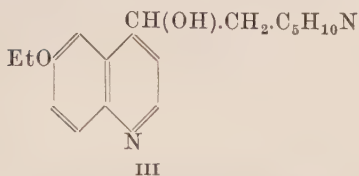
About the same time Howitz and Köpke [1] prepared a number of 8-quinolyl ketones and the corresponding carbinols, and Rabe and Pasternack repeating Remfry and Decker's work under different conditions added some further members to the series of 4-quinolyl alkyl ketones,[2] and also found [3] that substances of this type could be made by Claisen's method, condensing ethyl quinolinecarboxylates with ethyl esters of the fatty acids and hydrolysing the products with 25 per cent. sulphuric acid, thus ethyl cinchoninate and ethyl acetate yielded ethyl 4-quinoloylacetate, which hydrolysed to 4-quinolyl methyl ketone.

$$C_9H_6N.CO.CH_2.COOEt + H_2O \rightarrow C_9H_6N.CO.CH_3 + C_2H_5OH + CO_2$$

Later on this method was developed [4] to yield substances of the type $Q.CHOH.CHR.N<$, one of the most interesting being ethyl 1-4′-quinoloylmethyl-5-ethylpiperidino-4-acetate, obtained by condensing 4-quinolyl-bromomethyl ketone hydrobromide with ethyl cincholoiponate, which on reduction yields the secondary alcohol represented by the following formula :

$$CO_2Et.CH_2.CH{<}{CHEt.CH_2 \atop CH_2{-}CH_2}{>}N.CH_2.CH(OH).C_9H_5N$$
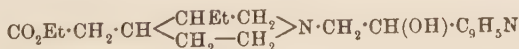
[1] *Annalen*, 1913, **396**, 38.
[2] *Berichte*, 1913, **46**, 1026. *Cf. ibid.* 1912, **45**, 2163.
[3] *Ibid.* p. 1032.
[4] Rabe, Pasternack and Kindler, *Berichte*, 1917 **50**, 144. *Cf.* German Patent 330,813 (*Chem. Soc. Abstr.* 1917 [i], 284).

Using the same method Rabe, Kindler and Wagner,[1] have prepared vinyl-free quinatoxines and quinaketones by condensing quinolinecarboxylates with ethyl β-4-piperidylpropionate. Thus ethyl N-benzoyl-β-4-piperidylpropionate condenses with ethyl cinchoninate to give a product, which on hydrolysis furnishes 9-rubatoxanone (vinyl-free cinchonicine). This yields an 8-bromo-derivative (the N-bromo-derivative may also be used, see p. 165), which on treatment with alkali furnishes 9-rubanone (vinyl-free cinchoninone). This series of changes may be graphically represented thus : the corresponding synthesis already referred to (p. 165) of dihydrocinchonicine and dihydrocinchoninone being added for comparison.
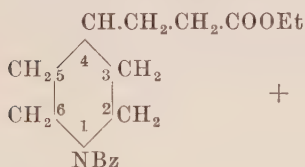
Ethyl N-*benzoyl-β-4-piperidylpropionate* Ethyl *cinchoninate*
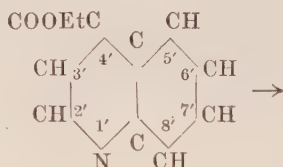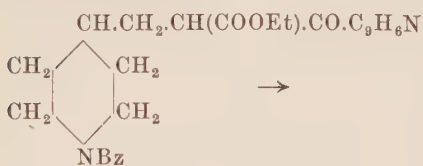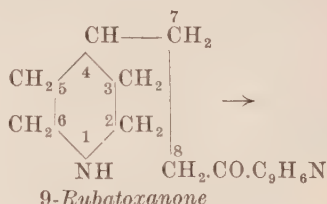
β-*Ketonic ester* 9-*Rubatoxanone*
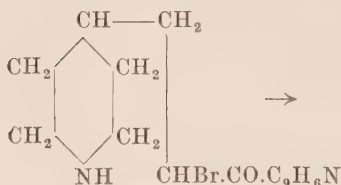
8-*Bromo-9-rubatoxanone* 9-*Rubanone*
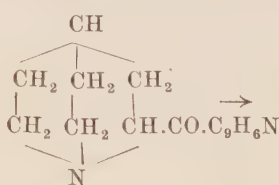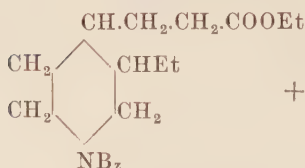
Ethyl *benzoylhomocincholoipon* Ethyl *cinchoninate*

CH.CH$_2$.CH(COOEt).CO.C$_9$H$_6$N

CH————CH$_2$

<table>
<tr><td>CH$_2$</td><td>CHEt</td></tr>
<tr><td>CH$_2$</td><td>CH$_2$</td></tr>
</table>

NB$_z$

$\rightarrow$

<table>
<tr><td>CH$_2$</td><td>CHEt</td></tr>
<tr><td>CH$_2$</td><td>CH$_2$</td></tr>
</table>

NH   CH$_2$.CO.C$_9$H$_6$N

$\rightarrow$

β-Ketonic ester   *Dihydrocinchonicine*

CH——CH$_2$

EtCH   CH$_2$

CH$_2$ CH$_2$

NH   CHBr.CO.C$_9$H$_6$N

CH

Et.CH   CH$_2$ CH$_2$

CH$_2$ CH$_2$ CH.CO.C$_9$H$_6$N

N

8-Bromodihydrocinchonicine   *Dihydrocinchoninone*
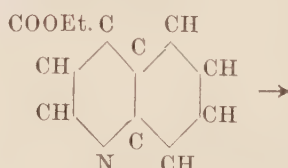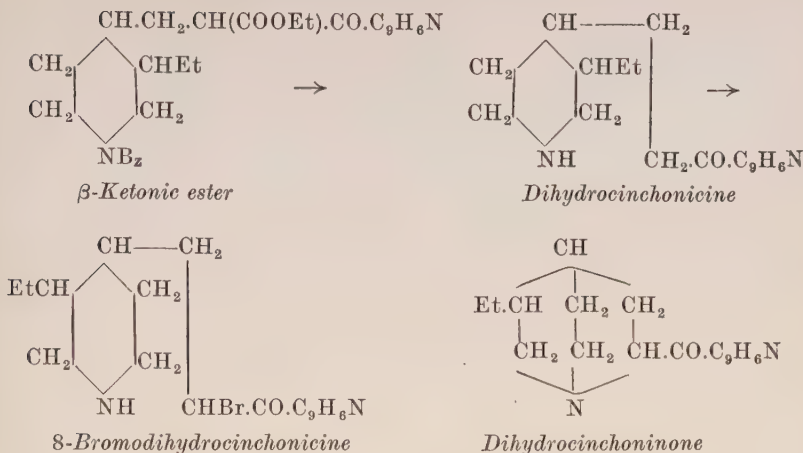
More recently Ruzicka [1] has prepared a series of "monocyclic cinchona alkaloids" by condensing esters of quinolinecarboxylic acids with alkyl-2-piperidones to form compounds of type I. These, on hydrolysis with hydrochloric acid, yield "aliphatic quinatoxins" (formulæ II and III), which, by the action of bromine followed by elimination of hydrogen bromide, yield "quinaketones," but the final step, reduction to a substance represented by formula IV has not yet been achieved.

$$C_9NH_6 \cdot CO_2Et + CH_2 <^{CH_2 \cdot CH_2}_{CO \cdot NMe}> CH_2 \longrightarrow \quad C_9NH_6 \cdot CO \cdot CH <^{CH_2 \cdot CH_2}_{CO \cdot NMe}> CH_2 \longrightarrow$$
$$\text{(I.)}$$

$$C_9NH_6 \cdot CO \cdot CH(CO_2Et) \cdot [CH_2]_3 \cdot NHMe \longrightarrow C_9NH_6 \cdot CO \cdot [CH_2]_3 \cdot NHMe.$$
$$\text{(II.)} \qquad\qquad\qquad \text{(III)}$$

$$C_9NH_6 \cdot CH(OH) \cdot CH <^{NMe \cdot CH_2}_{CH_2 - CH_2}$$
$$\text{(IV)}$$
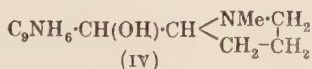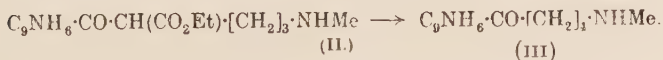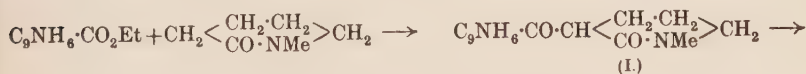
Karrer [2] has prepared a series of substances in which the piperidine ring is replaced by pyrrole, and the carbinol group is attached directly to both nuclei as in quinine and cinchonine. One of these 4-(6-methoxyquinolyl)-2-pyrryl carbinol (1), obtained by reducing the corresponding ketone, prepared by the interaction of quinolyl

[1] *Helv. Chim. Acta.* 1921, **4,** 472, 482, 486.
[2] *Berichte,* 1917, **50,** 1499.

chloride hydrochloride with magnesium pyrryl iodide, was found
to possess a slight antipyretic action, which would probably be
enhanced by reduction of the pyrrole ring when its analogy with
the cinchona alkaloids (*e.g.*, quinine (II) would be more complete.

$$N\!\!<^{C_6H_3(OMe)}_{CH-\!\!-\!\!-CH}\!\!>C\cdot CH(OH)\cdot C\!\!<^{CH-CH}_{NH\cdot CH'}$$

(I) 4-(6-*methoxyquinolyl*)-2-*pyrryl carbinol*

$$N\!\!<^{C_6H_3OMe}_{CH-\!\!-CH}\!\!>C.CHOH.CH\!\!<^{CH_2-CH_2}_{N-\!\!-CH_2}\!\!>CH.C_2H_4$$
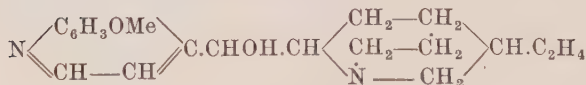
(II) *Quinine*

Modified Cinchona Alkaloids

Apart from the preparation of nearly tasteless derivatives of
quinine, such as the tannate, carbonate, and ethyl carbonate, very
little was done in the direction of modifying it with a view to im-
proving and extending its therapeutic action until 1891, when
Grimaux and Arnaud [1] prepared from cupreine a series of higher
homologues of quinine which proved to be somewhat more active
febrifuges than the natural alkaloid.[2] In these substances the
group R in the general formula becomes $-OC_2H_5.-OC_3H_7.$
$-OC_5H_{11}$, etc., instead of $-OH$ as in cupreine, and $-OCH_3$ as in
quinine. The discovery that the natural cinchona alkaloids could
be hydrogenated by the catalytic process, and that hydroquinine
was in some respects superior in action to quinine, led to increased
attention being given to the reduced alkaloids and, in particular, to
hydrocupreine, which could be alkylated just like the parent alkaloid,
and in this way a new series of derivatives was built up differing from
Grimaux and Arnaud's preparations by two atoms of hydrogen due
to reduction of the vinyl to the ethyl group (R') in the general
formula. In this way the very important alkylhydrocupreines were
made, which according to Bieling [3] and Schäffer,[4] become more
active with increasing weight of the substituent alkyl, maximum
activity being reached according to the former author with *iso-*

---

[1] *Compt. rend.* 1891, **112**, 774, 1364 ; 1892, **114**, 672.
[2] Spiegel, " *Chemische Konstitution und physiologische Wirkung*,"
1909.
[3] *Biochem. Zeitschr.* 1918, **85**, 188.
[4] *Berl. Klin. Woch.* 1917, **54**, 885.

octylhydrocupreine, while Schäffer places the maximum still higher in the series.

$$CH(4)$$
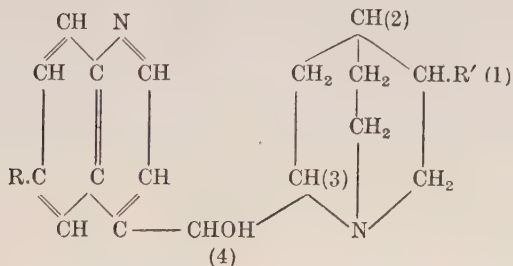
The best-known of these alkylhydrocupreines are the ethyl-, *iso*amyl- and *iso*octyl-derivatives, known commercially as "opto-quin," "eucupin" and "vuzin," respectively. The latter is stated to have been largely used by the Germans as a wound disinfectant during the Great War. Hydrocupreidine, the dextro-isomeride of hydrocupreine has also been used as the starting-point of a similar dextro-series of higher homologues of quinine. All these substances are made by demethylating hydroquinine or hydroquinidine and then alkylating the resulting dihydro-hydroxy base so that in them R′ in the general formula is —$CH_2.CH_3$, whilst R is —OH in hydro-cupreine and hydrocupreidine, and —OAlk in the case of the two series of ethers, whilst the difference in the optical activity of the two series depends on carbon atoms (3) and (4).

As already explained the cinchona alkaloids on prolonged heating with dilute acetic acid are converted into the "quinatoxines" cinchonicine, quinicine, cupreicine, and a similar change occurs with the hydrogenated bases, hydrocupreine and hydrocupreidine forming hydrocupreicine. This in turn can be alkylated, producing a new series, which are homologues of quinicine. The following formula represents these products :
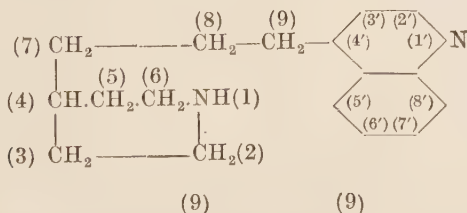
with the modifications that $\overset{(9)}{CH_2}$ becomes $\overset{(9)}{CO}$, carbon atom (6′) has

an —OH group in cupreicine and an —OAlk group in the alkyl ethers and carbon atom (3) an ethyl group, in the hydrocupreicines. The members of this series present no great advantage over the quinines and quinidines and their hydro-derivatives as regards their action on bacteria and protozoa, but the anæsthetic action, which is already well developed in "eucupin" (*iso*amylhydrocupreine) and *iso*amylhydrocupreidine becomes markedly greater, eucupinotoxin (*iso*amylhydrocupreicine) being from forty to fifty times more powerful as an anæsthetic than cocaine.[1] Some attention has also been given to the secondary alcohols produced by the reduction of the quinatoxines (in these $CH_2(9)$ becomes —CHOH—, the carbon atom becoming asymmetric. In this way Heidelberger and Jacobs [2] have prepared *d*-dihydrocinchonicinol (3-ethyl-9-hydroxy-rubatoxan) sulphate, $B_2.H_2SO_4.2H_2O$, m.p. 223°–224° (*dry*), $[\alpha]_D^{29} + 63.6°$ in water, and the *l*-isomeride, $B_2.H_2SO_4$, m.p. 232°–234°, $[\alpha]_D^{32} - 57.3°$ from cinchonicine; from quinicine *d*-dihydroquinicinol (3-ethyl-9-hydroxy-6'-methoxy-rubatoxan), m.p. 80°, $[\alpha]_D^{26°} + 87.1°$; nitrate, m.p. 115° (*dry*), dihydrochloride, m.p. 212°–214°, and the *l*-isomeride in the form of the dihydrochloride, m.p. 170°, $[\alpha]_D - 117.7°$. The ethyl ether of dihydrocupreicinol obtained by reducing ethyl-cupreicine crystallises from alcohol, on addition of water, in flattened needles, m.p. 105°–110°, $[\alpha]_D^{24.5}$ in dry alcohol ($c = 1.018$).

Giemsa and Halberkann [3] and Heidelberger and Jacobs [4] have also prepared nitro-, amino-, azo- and dihydroxy-derivatives of the hydrogenated alkaloids. Nitration is assumed to take place in position 5' in the quinoline nucleus. Cupreine, hydrocupreine, hydrocupreidine and some of the amino alkaloids yield dyes when coupled with diazotised aromatic amines.[5] The two latter authors [6] have also made a number of quaternary salts of the natural alkaloids and their hydro-derivatives, whilst they and other investigators [7] have isolated a large number of the more or less completely reduced

[1] Morgenroth, *Ber. Deut. pharm. Ges.* 1919, **29**, 233.

[2] *Journ. Amer. Chem. Soc.* 1922, **44**, 1098. *Cf.* German Patent 330,813 (*Chem. Soc. Abstr.* 1921 [i], 355).

[3] *Berichte*, 1919, **52**, 906 ; 1920, **53**, 732 ; also Howard, Blagden and Nierenstein, British Patent 182,986.

[4] *Journ. Amer. Chem. Soc.* 1920, **42**, 1481 ; 1922, **44**, 1073.

[5] H. and J. *ibid.* 1919, **41**, 2131. *Cf.* also 1920, **42**, 2278 ; 1922, **44**, 1073 ; and German Patent 379,880.

[6] *Ibid.* 1919, **41**, 2090.

[7] G. and H. *Berichte*, 1921, **54**, 1167, 1189 ; H. and J. *Journ. Amer. Chem. Soc.* 1920, **42**, 1489. *Cf.* Freund and Bredenburg, *Annalen*, 1914, **407**, 43 ; Skita and Brunner, *Berichte*, 1916, **49**, 1597 ; Norwall, *Berichte*, 1896, **29**, 801 ; Königs, *ibid.* 1896, **29**, 372.

alkaloids, obtained by drastic reduction of the natural and hydrogenated alkaloids and in which the secondary alcohol group has disappeared and the quinoline group is partly or wholly reduced, forming the hydrodeoxy bases.   While it is too early to say that any of these products are " modified " in the direction of therapeutic improvement on quinine itself, they are mentioned here as some of them have been protected by patents,[1] and many of them have avowedly been prepared for therapeutic experimental work.

A number of interesting observations has been made quite recently on the oxidation of cinchona alkaloids with hydrogen peroxide.   In this way Speyer and Becker [2] obtained oxides from quinine, quinidine and cupreine and their hydro-derivatives, but not from cinchonine.   The oxygen atom is believed to be attached directly to the N of the quinuclidine ring making it pentavalent. The oxides are well crystallised, yield salts, liberate iodine from potassium iodide solution, and are reconverted into the original alkaloids by reduction with sulphurous acid.   Fränkel and co-workers [3] suppose that oxides of this type may be intermediate products in the formation of quiteninone, $C_{19}H_{20}O_4N_2$ (needles, m.p. 156°), which they observed on oxidising quinine sulphate with hydrogen peroxide in presence of copper or ferrous sulphate as a catalyst.   Advantage has been taken of this method to increase the yield of alkyl ethers of hydrocupreine by first converting these bases into the oxides and then alkylating these ; the nitrogen atom being protected there is no loss due to alkylation of the tertiary nitrogen.   The alkylated oxides are finally reduced by sulphurous acid.[4]

Physiological Action of the Chief Cinchona Alkaloids

Of the natural cinchona alkaloids only four have come into extensive use in medicine, viz., quinine, quinidine, cinchonine and cinchonidine, and of these quinine far transcends the others in importance.   It is usually employed in the form of the neutral sulphate, but considerable quantities of the neutral hydrochloride, the acid sulphate, and acid hydrochloride are also used, the two latter especially for injection owing to their ready solubility.   In

[1] Cf. e.g., German Patents 335,113 ; 338,738 ; 339,947 (Chem. Soc. Abstr. 1921 [i], 515 ; 1922 [i], 46) ; British Patent 182,986 (ibid. 1922 [i], 853).

[2] Berichte, 1922, 55, 1321.

[3] Ibid. p. 3931.

[4] German Patent 344,140 (Chem. Soc. Abstr. 1922 [i], 948).

addition a large number of the salts with organic acids are employed
for special purposes as well as esters such as the ethyl carbonate
(euquinine) and carbonate (aristoquinine).

Quinine is frequently called a protoplasm poison because of its
action on undifferentiated protoplasm. This action is, however,
selective, most but not all protozoa being affected. The alkaloid
also retards the action of some enzymes, especially of the oxidases.
It has a well-marked local anæsthetic action, and, in combination
with carbamide, which increases its solubility, is used in practice as
a local anæsthetic.

The first use of quinine in medicine was as a specific for malaria,
and its use for this purpose as a remedy and also as a prophylactic
has constantly increased.   Its value in this disease is due to its
direct action on the plasmodium, which causes malaria in man.[1]   It
has long been known in a general way that there were noticeable
differences in the value of the chief cinchona alkaloids in the treat-
ment of malaria,[2] and in 1919 Morgenroth[3] pointed out that though
chemotherapeutic action towards bacteria and protozoa, and the
power of producing anæsthesia are common to the natural alkaloids,
their hydro-derivatives and the isomeric quinatoxines, these pro-
perties vary quantitatively both with variation in structure and
with the spatial arrangement of the component groups. The
importance of this last factor in the tropane group has already been
referred to (p. 116).   In the cinchona group it has been investigated
especially by Acton,[4] who finds that whilst quinine, or better
hydroquinine (lævorotatory) is a specific for malignant tertian
malaria, quinidine (dextrorotatory) is more efficient in benign
tertian malaria, and that on the whole the dextrorotatory alkaloids
are more toxic to mice and protozoa, have a greater inhibitory effect
on the action of digestive enzymes, and are more powerful in their
action on blood pressure and uterine muscle, but show less anæsthetic
action than the lævorotatory alkaloids.   Quinidine has in the last
few years come into use for restoring normal cardiac rhythm in cases
of auricular fibrillation.

With regard to the modified cinchona alkaloids in general, they

[1] For useful accounts of the pharmacology of quinine and its
derivatives, see Dixon, *Brit. Med. Journ.*, July 24th, 1920, p. 113,
and Acton ; *Lancet*, January 21st, 1922, p. 124.

[2] McGilchrist, *Ind. Journ. Med. Research*, 1914, **2**, 315, 336, 518 ;
1915, **2**, 888.

[3] *Ber. Deut. pharm. Ges.*, 1919, **29**, 233.

[4] *Lancet*, January 21st, 1922, p. 124.

become more toxic to mammals, protozoa, and bacteria with hydrogenation of the vinyl group and replacement of the methoxyl group of quinine and quinidine by higher alkyloxy groups, at least up to the *iso*octyl ether, but this action remains selective, as with quinine though differently so, thus ethyl hydrocupreine hydrochloride is toxic to pneumococcus at 1 in 500,000, but only at 1 in 500 to staphylococcus. It has been employed in pneumonia, but requires caution in use as it may produce blindness.[1] *iso*Octylhydrocupreine hydrochloride (Vuzin) is said to have been largely used by the Germans for treating septic wounds during the War. The power of inducing local anæsthesia also increases with hydrogenation and with increase in weight of the alkyloxy substituent, *iso*amylhydrocupreine and *iso*amylhydrocupreidine being respectively about twenty and ten times as powerful as cocaine, and is still further increased by the change to the quinicine (quinotoxin) structure *iso*amylhydrocupreicine being about forty times as powerful as cocaine in producing corneal anæsthesia.[2]

Miscellaneous Cinchona Alkaloids

Quinamine, $C_{19}H_{24}O_2N_2$, was found by Hesse in *Cinchona succirubra*, and in small quantity in many varieties of cinchona bark, but especially *C. Ledgeriana*.[3] *(Contd.* p. 176.)

Isomerides and Derivatives of Quinamine

Name and formula	Formation	Properties	Reference
Quinamidine, $C_{19}H_{24}O_2N_2$	Action of tartaric acid solution on quinamine at 130°.	Crystals, m.p. 93°, $[a]_D + 4\cdot5°$ in alcohol.	Hesse, *Annalen*, 1881, **207**, 299.
Quinamicine, $C_{19}H_{24}O_2N_2$	By evaporating quinamine with sulphuric acid in alcohol.	Crystals, m.p. 109°, $[a]_D + 38\cdot1°$.	
Protoquinamicine, $C_{19}H_{24}O_2N_2$	By heating quinamine sulphate at 120°.	Amorphous.	
Apoquinamine, $C_{19}H_{22}ON_2$	By heating quinamine or quinamicine with hydrochloric acid.	Crystallises in leaflets or prisms, m.p. 114°, lævorotatory.	

[1] Dixon, *Brit. Med. Journ.*, July 24th, 1920, p. 113. *Cf.* Schäffer, *Bio-chem. Zeit.* 1917, **83**, 269; Bieling, *ibid.* 1918, **85**, 188.

[2] Morgenroth, *loc. cit.*

[3] *Berichte*, 1877, **10**, 2157; *Annalen*, 1873, **166**, 266; 1881, **207**, 288.

The alkaloid crystallises from dilute alcohol in long silky anhydrous needles, m.p. 172°, $[\alpha]_D + 93 \cdot 4°$ in chloroform, $+ 104 \cdot 5°$ in alcohol, is slightly soluble in cold water (1 in 1516 at 16°), but more so in alcohol (1 in 105 of 80 per cent. at 20°), ether (1 in 32 at 20°), benzene or light petroleum. The salts are crystalline.

Minor Cinchona Alkaloids.

Name and Formula	Source	Properties	References
Conquinamine, $C_{19}H_{24}O_2N_2$	*C. succirubra*, *C. Ledgeriana*, etc.	Triclinic crystals, m.p. 121°, $[\alpha]_0 + 204 \cdot 6°$ in alcohol. Crystalline salts.	Hesse, *Annalen*, 1881, **209**, 62. Oudemans, *Ibid.*, p. 38.
Paricine, $C_{16}H_{18}ON_2 \cdot \frac{1}{2}H_2O$	*C. succirubra* from Darjeeling.	M.p. 130°, amorphous salts, $[\alpha]_D + 0$.	Hesse, *Annalen*, 1873, **166**, 263.
Dicinchonine (Dicinchonicine), $C_{38}H_{44}O_2N_4$.	*C. rosulenta* and *C. succirubra*.	Amorphous, dextrorotatory.	Hesse, *ibid.*, 1885, **227**, 154.
Diconquinine (Diquinicine), $C_{40}H_{46}O_4N_4$	" Quinoidine," p. 136.	Amorphous, dextrorotatory.	Hesse, *Berichte*, 1877, **10**, 2155.
Javanine.	*C. Calisaya*, var. *Javanica*.	Rhombic plates.	Hesse, *Berichte*, 1877, **10**, 2162.

Alkaloids of Cusco Bark (*Cinchona cordifolia*, var. *Pelletieriana*).

Name and Formula	Properties	References
Aricine (Quinovatine), $C_{23}H_{26}O_4N_2$.	Prisms, m.p. 188°, $[\alpha]_D - 58°$ 18′ in alcohol. Oxalate and acetate insoluble in water. Gives a green colour with nitric acid.	Pelletier & Coriol, *Journ. Pharm.*, 1829, **15**, 565 ; Hesse, *Annalen*, 1873, **166**, 259 ; 1876, **181**, 58 ; 1877, **185**, 310 ; Moissan and Landrin, *Bull. Soc. Chim.*, 1890 [iii.], **4**, 258.
Cusconine, $C_{23}H_{26}O_4N_2 \cdot 2H_2O$.	Leaflets, m.p. 110° (*dry*), $[\alpha]_D - 54 \cdot 3°$ in alcohol.	Lever-Kohn, 1829 ; Hesse, *Annalen*, 1877, **185**, 301.
Cusconidine.	Amorphous.	Hesse, *loc. cit.*
Cuscamine.	Prisms, m.p. 218°.	Hesse, *ibid.*, 1880, **200**, 304.
Cuscamidine.	—	

ALKALOIDS OF *REMIJIA PURDIEANA*

The bark of *Remijia Purdieana*, a tree nearly related to that yielding cuprea bark (p. 146), yields a little cinchonine and a series of other alkaloids, including concusconine, chairamine, conchairamine, chairamidine, conchairamidine and cinchonamine for which Hesse [1] gives a scheme of separation.

Cinchonamine, $C_{19}H_{24}ON_2$, first isolated by Arnaud,[2] crystallises in triboluminescent,[3] orthorhombic needles, m.p. 194°, $[\alpha]_D + 121 \cdot 1°$ in alcohol, insoluble in cold water, soluble in alcohol (1 in 31·6 of 90 per cent. at 17°), easily in hot chloroform or benzene. No methoxyl is present. It forms a series of crystalline double chlorides with cadmium, zinc or copper,[4] does not give the thalleioquin reaction, and solutions of its sulphate are not fluorescent. It is diacidic and forms two series of salts; the only important salt is the nitrate, $B.HNO_3$, crystallising in minute prisms, m.p. 196°, insoluble in water. Cinchonamine hydrochloride, $B.HCl$, laminæ, or $B.HCl.H_2O$, cubical crystals, has been suggested as a suitable salt for use in the estimation of nitrates.[5] The physiological action of cinchonamine is similar to that of quinine, but it is a more potent antipyretic and is also poisonous.

When warmed with strong nitric acid the alkaloid furnishes dinitrocinchonamine. It gives an amorphous, monoacetyl derivative, and combines with methyl iodide to form a methiodide crystallising in prisms, m.p. 208°, which with silver oxide gives methylcinchonamine, an amorphous powder, from which no well-defined derivatives have so far been obtained.

Concusconine, $C_{23}H_{26}O_4N_2$, is best crystallised from hot alcohol. It forms monoclinic needles, $[\alpha]_D^{15} + 40 \cdot 8°$ (Léger) in alcohol, $[\alpha]_D + 19° \, 34'$ (Howard and Chick)[6], melts at 144°, and remelts at 206°–208°, is insoluble in water, very sparingly in cold alcohol, easily soluble in ether or chloroform. It dissolves in concentrated sulphuric acid with a bluish-green colour, becoming olive-green on warming. Concusconine contains two methoxyl groups. The salts are amorphous. The base reacts with methyl iodide, forming α- and

[1] *Annalen*, 1884, **225**, 211.

[2] *Compt. rend.* 1881, **93**, 593 ; 1883, **97**, 174 ; Hesse, *Annalen*, 1884, **225**, 218.

[3] Tschugæff, *Berichte*, 1901, **34**, 1824.

[4] Boutrioux and Genvresse, *Compt. rend.* 1897, **125**, 467.

[5] Howard and collaborators, *J. Soc. Chem. Ind.* 1905, **24**, 1281 ; 1909, **28**, 53.

[6] *J. Soc. Chem. Ind.* 1905, **24**, 1281 ; 1909, **28**, 53.

β-methiodides, which in turn furnish α- and β-methohydroxides, the former crystalline, the latter amorphous.

The chief characters of the remaining bases from this bark are stated in the following table :

Name and formula	Crystalline form	Optical rotation $[a]_D$	Colour reactions
Chairamine, $C_{22}H_{26}O_4N_2.H_2O$	Needles or prisms, m.p. 233° (*dry*)	Dextrorota-tory	A solution in acetic acid gives a dark green colour with nitric acid
Conchairamine, $C_{22}H_{26}O_4N_2.H_2O$	Prisms, m.p. 120° (*dry*)	+ 68·4° at 15° in alcohol	As above ; also sul-phuric acid gives a brown colour, be-coming green
Chairamidine, $C_{22}H_{26}O_4N_2.H_2O$	Amorphous	+ 7·3° at 15° in alcohol	Sulphuric acid gives a green colour. Nitric acid colours a hydrochloric acid solution green
Conchairamidine, $C_{22}H_{26}O_4N_2.H_2O$	Crystalline, m.p. 114° (*dry*)	— 60° at 15° in alcohol	Sulphuric acid gives a deep green colour

ALKALOIDS OF STRYCHNOS SPECIES

Strychnine and brucine, the only important alkaloids derived from this genus of plants, occur most abundantly in nux-vomica seeds (*Strychnos Nux-vomica*) found in the East Indies, and Ignatius beans (*S. Ignatii*) of the Philippine Islands. Both nux-vomica seeds and Ignatius beans contain 2·0 to 3·0 per cent. of total alkaloids, but rather less than half is strychnine in the former, and up to two-thirds in the latter, the rest being brucine. These alkaloids also occur in the leaves, bark, wood, fruit pulp and root of *Strychnos Nux-vomica*, and according to van Boorsma the leaves contain a third alkaloid, strychnicine. *S. Tieuté* seeds, found in Java, contain 1·4 per cent. of strychnine, with traces of brucine. The wood and bark of *S. ligustrina* contain 2·2 and 7·3 per cent. respectively of brucine, but are free from strychnine.[1] The seeds

[1] Greenish, *Pharm. Journ.* 1879 [iii], **9,** 1013.

PLATE III.
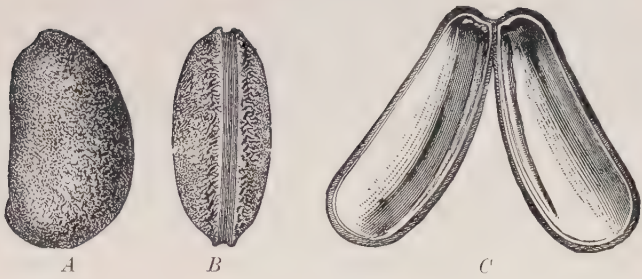
FIG. 1.—Calabar bean (p. 415). *A*, side view. *B*, edge, showing the long hilum. *C*, seed split open. (Maisch.)
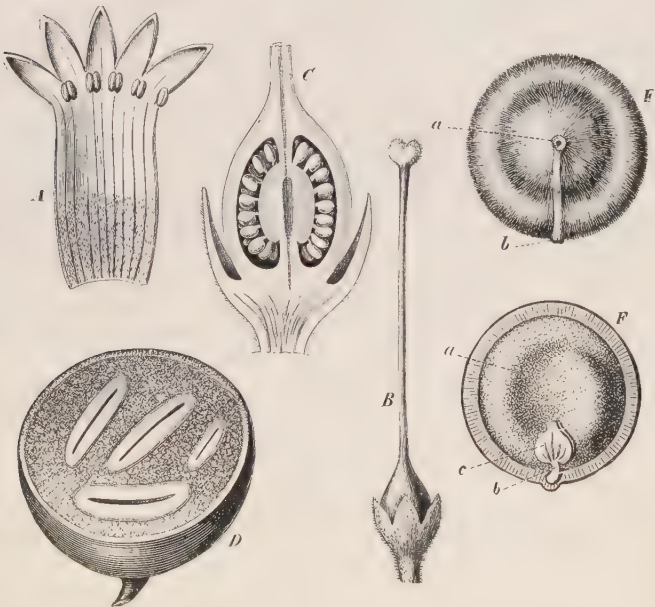
FIG. 2.—Nux Vomica. *A*, flower opened, magnified. *B*, ovary with style, magnified. *C*, ovary, cut longitudinally, more highly magnified. *D*, ripe fruit, cut transversely, showing seeds; reduced to about one-half. *E*, seed, entire, natural size. *F*, the same, cut vertically. (Luerssen.)
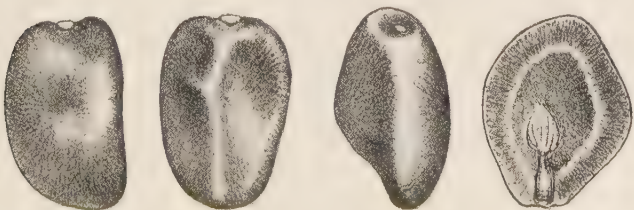
FIG. 3.—Ignatius Beans. Natural size. (Bentley and Trimen.)

of *S. Rheedei*, an Indian species, contain brucine only, and this is also the case with *S. aculeata* of West Africa.   *S. Henningsii* of South Africa contains a bitter alkaloid not identical with either strychnine or brucine.[1]   Among species free from poisonous alkaloids [2] are *S. potatorum*, the seeds of which are highly mucilaginous, and are used for clearing drinking water in India.

The *Strychnos* species referred to in the foregoing paragraph are mainly inhabitants of the East Indies.   The South American species, such as *S. toxifera* and *S. Castelnœi*, yield the highly toxic product " Curare " or " Woorari " (*see* p. 191).

Estimation of Alkaloids.   For the estimation of strychnine in nux-vomica seeds, the following process is given in the British Pharmacopœia, 1914 : 7·5 grm. of seeds in No. 60 powder are shaken frequently during half an hour with a mixture of chloroform 25 c.c., ether 50 c.c., and solution of ammonia 5 c.c., and 50 c.c. of the clear solution transferred to a separator and extracted with acid three times, 10 c.c. of *N*-sulphuric acid being used each time.   The combined acid liquids are made alkaline with ammonia and the liberated alkaloids extracted with chloroform using 10, 5 and 5 c.c. of this solvent.   The chloroform is distilled off and the residue of crude alkaloid dissolved in 5 c.c. of diluted sulphuric acid with 10 c.c. of water.   This solution is warmed to 50° and 3 c.c. of a mixture of nitric acid and water (equal volumes) added and set aside for ten minutes.[3]   The solution is transferred to a separator, made alkaline with caustic soda solution and the alkaloid extracted with chloroform using 10, 5 and 5 c.c. in succession.   The combined chloroform solution is washed with 5 c.c. of water, the chloroform evaporated, 5 c.c. of alcohol being added towards the end and the residue dried at 100° and weighed.   This weight multiplied by 20 gives the weight of strychnine in 100 grm. of the drug ; it should not be less than 1·25 per cent.

[1] *Bull. Imp. Inst.* 1916, **14,** 33.
[2] Flückiger, *Arch. Pharm.* 1892, **230,** 343.
[3] To destroy the brucine.   For observations on this method *see* *Ned. Tydschr. Pharm.* 1889, **11,** 1 ;   *Pharm. Journ.* 1900 [iv], **11,** 82 ; *Arch. Pharm.* 1902, **240,** 641 ;   *Analyst,* 1905, **30,** 261 ;   *Amer. J. Pharm.* 1903, **75,** 253 ;   *Journ. Soc. Chem. Ind.* 1906, **25,** 512 ;   *Amer. J. Pharm.* 1907, **79,** 1 ;   *Analyst,* 1914, **39,** 81 ;   *Chem. Soc. Abstr.* 1914 [ii], 307 ; *Pharm. Journ.* 1914, **93,** 120 ;   *ibid.* 1916, **97,** 458 ;   *Zeit. angew. Chem.* 1918, **31** [i], 124.   For information regarding the ferrocyanide method of separating strychnine from brucine, *see* Dunstan and Short, *Pharm. Journ.* 1883 [iii], **14,** 292 ;   and *Arch. Pharm.* 1887 [iii], **25,** 313 ;   *Pharm. Journ.* 1885 [iii], **16,** 447 ;   *Ned. Tydschr. Pharm.* 1889, **11,** 1 ;   *Pharm. Journ.* 1900 [iv], **11,** 82 ;   *Analyst,* 1914, **39, 81.**

In the United States Pharmacopœia (9th Rev.) a process for the estimation of the total alkaloids only in the crude drug is given. Fifteen grammes of nux-vomica seeds in No. 40 powder are placed in a 250 c.c. flask with 150 c.c. of a mixture of chloroform (1 vol.), ether (2 vols.), shaken well, left to stand for ten minutes, and 10 c.c. of dilute ammonia solution added, and the whole shaken at intervals of ten minutes during two hours, and then allowed to stand ten hours. Twenty-five cubic centimetres of water are then added shaken well, and when the drug has settled 100 c.c. of the clear liquid are decanted (= 10 grm. of drug) and the alkaloids extracted as described under belladonna (p. 65). The residue is finally titrated by dissolving it in 10 c.c. of $N/10$ sulphuric acid and the excess of acid determined. Each cubic centimetre of $N/10$ sulphuric acid corresponds to 0·0364 grm. of total alkaloids. The seeds are required to contain 2·5 per cent. of total alkaloids, as determined by this process.

Strychnine, $C_{21}H_{22}O_2N_2$. This alkaloid was discovered by Pelletier and Caventou in 1817, and was investigated by Regnault,[1] who assigned to it the formula given above, which was confirmed by Nicholson and Abel in 1849.[2] For the extraction of strychnine and brucine the finely-ground *Strychnos* seeds may be mixed with 25 per cent. of their weight of slaked lime and made into a stiff paste with water. This is dried at 100°, powdered, and exhausted with hot chloroform by percolation. From this the alkaloids are removed by agitation with dilute sulphuric acid, which is then filtered, excess of ammonia added, and the precipitate extracted with 25 per cent. alcohol which dissolves the brucine and leaves most of the strychnine undissolved. The latter is purified by recrystallisation from alcohol, in which brucine is more soluble.

Strychnine crystallises in colourless rhombs, m.p. 268°, $[\alpha]_D$ — 132·07° in alcohol. According to Loebisch and Schoop it distils unchanged at 270° under 5 mm. pressure.[3] The base is slightly soluble in water (1 in 6400 at 25°, 1 in 3000 at 80°) or ether (1 in 5500 at 25°), more so in 90 per cent. alcohol (1 in 110 at 25° or 1 in 28 at 60°), or benzene (1 in 150 at 25°), readily so in chloroform (1 in 6 at 25°). The aqueous solution is alkaline and has a persistent bitter taste, even in a solution containing 1 part in 700,000 of water. It behaves as a monoacidic base ; the salts crystallise well. Three of

[1] *Annalen*, 1838, **26**, 17.
[2] *Journ. Chem. Soc.* 1850, **2**, 241
[3] *Monats.* 1885, **6**, 858.

them are used in medicine, viz., the nitrate, sulphate and hydro-chloride. Strychnine nitrate, $B.HNO_3$, colourless shining needles, soluble in water (1 in 42 at 25°), alcohol (1 in 120 at 25°), or chloro-form (1 in 156 at 25°); lævorotatory. The sulphate, $B_2.H_2SO_4$. $5H_2O$, forms colourless prismatic crystals, m.p. 200° (*dry*), and is soluble in water (1 in 31 at 25°), or alcohol (1 in 65 at 25°), less so in chloroform (1 in 325 at 25°). The hydrochloride, $B.HCl.2H_2O$, forms colourless, efflorescent, trimetric prisms, soluble in cold water (1 in 35) or alcohol (1 in 60). The aurichloride, $B.HAuCl_4$, crystal-lises from alcohol in orange-yellow needles. The hydriodide, $B.HI$. H_2O, is sparingly soluble in water as is also the periodide, $B.HI.I_2$; the latter crystallises from alcohol in reddish-brown prisms. The dichromate is very slightly soluble in cold water (1 in 1815 at 18°) and crystallises from boiling water in orange-yellow needles.

Strychnine is not coloured by sulphuric acid, even on warming. With nitric acid it gives a yellowish coloration, and the residue left on evaporating the liquid at 100° gives a reddish-purple colour with ammonia. A fragment of the alkaloid in a drop of sulphuric acid gives, with a crystal of potassium dichromate, manganese dioxide, ceric oxide, or potassium permanganate, stirred in it, a series of colours, beginning with blue, which gradually passes through violet and red to yellow.[1] The only other alkaloids which closely resemble strychnine in this respect are curarine and gelsemine. Certain other alkaloids give a somewhat similar colour reaction, but most of these are also coloured by sulphuric acid alone. Brucine gives a deep red colour when oxidised, *e.g.*, with nitric acid, and this is apt to obscure the colour change produced by strychnine, so that if brucine is present it should first be eliminated by treatment with potassium ferrocyanide or nitric acid as described on p. 179. Organic matter also masks the reaction, and may be got rid of by warming with sulphuric acid and recovering the strychnine by adding water and ammonia and shaking out with chloroform.[2] Sulphuric acid containing vanadic acid gives with strychnine a deep bluish-violet colour, changing to purple and finally to red.[3]

Constitution of Strychnine. Although containing two atoms of nitrogen, strychnine behaves as a monoacidic base. Warmed with

[1] Marchand, *Journ. Pharm.* [iii], **4,** 200.
[2] For other interfering substances, *see* Mameli, *Chem. Soc. Abstr.* 1915 [ii], 113.
[3] Guerin, *J. Pharm. Chim.* 1914 [vii], **9,** 595.

a solution of sodium ethoxide it takes up a molecule of water [1] forming strychninic acid, $C_{21}H_{24}O_3N_2$, which crystallises in minute needles, m.p. 215°, is soluble in water, insoluble in ether or dry alcohol, but readily soluble in aqueous solutions of ammonium salts. It forms salts with mineral acids, but when warmed with excess of the latter, strychnine is reformed. Strychninic acid reacts with sodium nitrite and hydrochloric acid to form a nitrosoamine, $C_{21}H_{23}(NO)O_3N_2$, dissolves in alkaline solutions to form unstable salts, undergoes indirect esterification, and with methyl iodide yields methylstrychninic acid methiodide. These reactions indicate that strychninic acid is an iminocarboxylic acid produced by the hydration of a betaine group in strychnine :

$$N \vdots C_{20}H_{22}O\underline{\quad\quad}CO \qquad\qquad N \vdots C_{20}H_{22}O\underline{\quad\quad}COOH$$

Strychnine   *Strychninic acid*
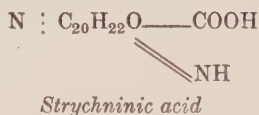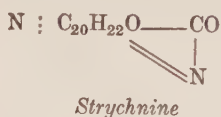
The nitrogen atom included in the betaine group is non-basic and this accounts for the monoacidic character of strychnine. When strychnine is warmed with a saturated aqueous solution of barium hydroxide at 140°, it is converted into *iso*strychninic acid, which has been isolated as the hydriodide (microscopic needles) and is readily distinguished from its isomeride by not giving strychnine when warmed with dilute acids. It furnishes a nitrosoamine, which is readily converted into a nitroso compound by alcoholic hydrogen chloride.[2] According to Bacovescu and Pictet,[3] *iso*strychnine (needles, m.p. 223°–224°) is formed when strychnine is heated in water at 160°–180°, or better with ammonia and methyl alcohol, and this with sodium ethoxide in alcohol yields *iso*strychninic acid.

Strychnine readily combines with methyl iodide, forming a methiodide, which is converted by silver oxide or baryta into strychninic acid methylhydroxide, and this, by the loss of a molecule of water gives methylstrychnine,[4] which is also formed when strychninic acid methiodide is treated with silver oxide.[5] Further, when methylstrychnine reacts with aqueous hydriodic acid it forms strychninic acid methiodide, and the latter on warming furnishes

[1] Loebisch and Schoop, *Monats.* 1886, **7**, 83 ; Tafel, *Annalen*, 1891, **264,** 50.

[2] Tafel, *Annalen*, 1891, **264,** 69.

[3] *Berichte*, 1905, **38**, 2787. *Cf.* Leuchs and Nitschke, *ibid.* 1922, **55,** 3171.

[4] Tafel, *ibid.* 1890, **23**, 2732.

[5] Tafel, *Annalen*, 1891, **264,** 50.

strychninemethiodide. This series of changes may be represented in the following way :

$$\longrightarrow MeI : N : C_{20}H_{22}O - CO \quad \longrightarrow \quad MeOH : N : C_{20}H_{22}O - CO \quad \longrightarrow$$
$$\diagdown |_{N} \qquad\qquad\qquad \diagdown |_{N}$$

Strychnine methiodide   *Strychnine methylhydroxide*

$$\longrightarrow MeOH : N : C_{20}H_{22}O - COOH \quad \longrightarrow \quad MeN : C_{20}H_{22}O - CO \overset{\displaystyle \longrightarrow O}{}$$
$$\diagdown NH \qquad\qquad\qquad\qquad \diagdown NH$$

Strychninic acid methylhydroxide   *Methylstrychnine*

$$MeI : N : C_{20}H_{22}O - COOH$$
$$\diagdown NH$$

Strychninic acid methiodide
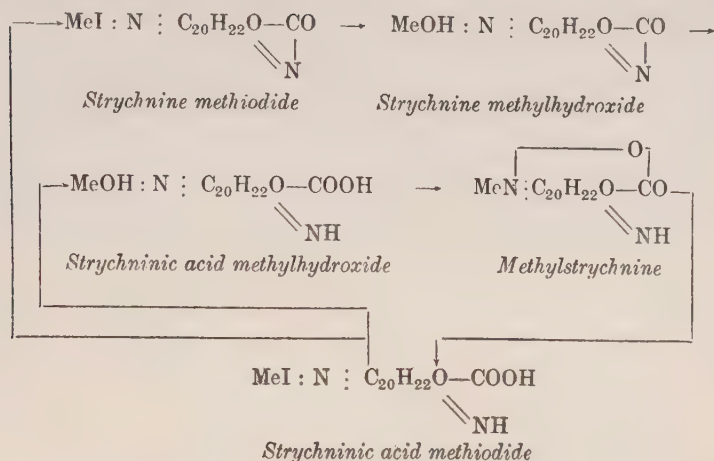
Methylstrychnine crystallises in long prisms, is soluble in water, gives the characteristic colour reactions of strychnine, and though not bitter, still exerts a physiological action like that of strychnine. It behaves as a secondary amine, and with methyl iodide gives a methiodide, which on heating with silver sulphate and barium hydroxide yields dimethylstrychnine.[1] This base is also produced from strychninic acid by conversion of the latter into the corresponding methiodide, which in presence of caustic soda and methyl iodide furnishes *N*-methylstrychninic acid methiodide : the latter readily loses a molecule of hydrogen iodide when warmed with silver oxide, forming the corresponding betaine, dimethylstrychnine.[2]

Dimethylstrychnine with nitrous acid yields nitrosodimethyl-strychnine, which exhibits the same peculiarities as nitrosodimethyl-aniline,[2] giving colouring matters by condensation with benzaldehyde, etc. Such behaviour is also characteristic of *N*-methyltetra-hydroquinoline whence Tafel suggested that this base is the nucleus of the strychnine molecule.

In like manner *iso*strychninic acid furnishes methyl*iso*strychnine (needles from water) and dimethyl*iso*strychnine (microscopic needles, from water). Similarly, this acid reacts with methyl iodide to form a *N*-methyl*iso*strychninic acid.

When strychnine is reduced with hydriodic acid and phosphorus, a crystalline product, desoxystrychnine, $C_{21}H_{26}ON_2$, is formed.

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[1] Tafel, *Berichte*, 1890, **23**, 2731.   [2] Tafel, *Annalen*, 1891, **264**, 66.

This substance gives the characteristic colour reactions of strychnine and contains unchanged the betaine group of the latter, since it reacts with sodium ethoxide forming desoxystrychninic acid. It also forms a methiodide, so that in the formation of desoxystrychnine no change has occurred in connection with the second nitrogen atom of strychnine. Desoxystrychnine must, therefore, be represented by the formula :

$$N \ \vdots \ C_{20}H_{26}\text{----}CO \quad \rightarrow \quad N \ \vdots \ C_{20}H_{26}\text{----}COOH$$
$$\diagdown N \qquad\qquad\qquad\qquad \diagdown NH$$

Desoxystrychnine   *Desoxystrychninic acid*
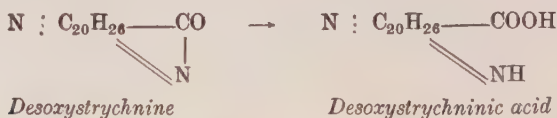
When solutions of desoxystrychnine sulphate are reduced electrolytically a dihydrostrychnoline, $C_{21}H_{28}N_2$, is formed, whilst the less reduced substance, strychnoline, $C_{21}H_{26}N_2$, is obtained when desoxystrychnine, dissolved in boiling amyl alcohol is treated with sodium. These reduction products show a gradual weakening of the specific physiological action of the parent alkaloid, dihydrostrychnoline being non-poisonous. A similar behaviour is exhibited by α-piperidone and its reduction product, piperidine ; the former exerts a strong tetanising action, whilst the latter is physiologically inactive.[1]

Strychnine, when reduced electrolytically [2] or by hydrogen in presence of palladium chloride,[3] furnishes a tetrahydro-derivative $C_{21}H_{26}O_2N_2$, together with strychnidine, $C_{21}H_{24}ON_2$, the latter being also formed by loss of water when tetrahydrostrychnine is warmed with mineral acids. Strychnidine closely resembles dihydrostrychnoline in properties, but still possesses the characteristic physiological action of strychnine. These reduction products may be represented thus :

$$N \ \vdots \ C_{20}H_{24}\text{----}CH_2 \qquad\qquad N \ \vdots \ C_{20}H_{26}\text{----}CH_2$$
$$\diagdown N \qquad\qquad\qquad\qquad\qquad \diagdown N$$

Strychnoline   *Dihydrostrychnoline*

$$N \ \vdots \ C_{20}H_{22}O\text{----}CH_2OH \qquad\qquad N \ \vdots \ C_{20}H_{22}O\text{----}CH_2$$
$$\diagdown NH \qquad\qquad\qquad\qquad\qquad \diagdown N$$

Tetrahydrostrychnine   *Strychnidine*
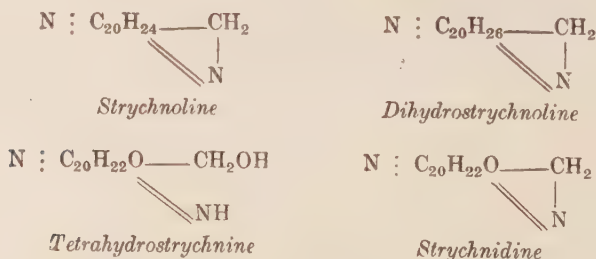
[1] Schotten, *Berichte*, 1888, **21**, 2244 ; Tafel, *Annalen*, 1892, **268**, 234 ; 1898, **301**, 285.

[2] Tafel and Naumann, *Berichte*, 1901, **34**, 3291. *Cf.* Leuchs, *ibid.* 1914, **47**, 536.

[3] Skita and Franck, *ibid.* 1911, **44**, 2862.

When strychnine is oxidised with chromic acid,[1] it furnishes an acid, $C_{15}H_{17}O_2N_2 \cdot COOH$, which on distillation with zinc dust yields carbazole (diphenylimide), which Loebisch and Malfatti also obtained by distilling strychnine with soda-lime.[2] Perkin and Robinson [3] first called attention to the important bearing which this formation of carbazole and carbazole derivatives has on the constitution of strychnine, and pointed out that the results indicated above show that strychnine must contain both quinoline and carbazole nuclei :
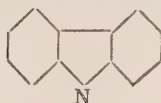
Since strychnine can be sulphonated [4] and nitrated [5] the quinoline nucleus probably contains a benzene ring, and to account for the reduced character of strychnine it must be assumed that the pyridine ring of the quinoline nucleus, and probably also the carbazole nucleus are almost completely reduced. Further, as the N atom in the quinoline nucleus is in a betaine group, it follows that the N atom in the carbazole nucleus must be that which is basic and tertiary. Of the possible ways of combining these two nuclei to give the molecule $C_{21}H_{22}O_2N_2$, Perkin and Robinson [6] regard the following as the most probable :
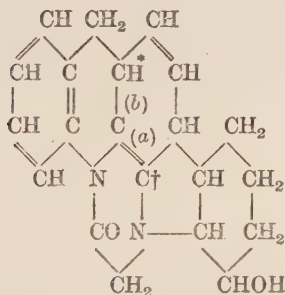
Strychnine (Perkin and Robinson)   *Desoxystrychnine*
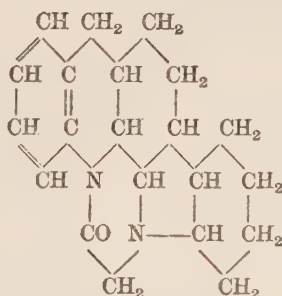
[1] Hanssen, *ibid.* 1884, **17**, 2849 ; 1885, **18**, 777, 1917 ; 1887, **20**, 451.

[2] *Monats.* 1888, **9**, 629.

[3] *Trans. Chem. Soc.* 1910, **97**, 309.

[4] Stöhr, *Berichte*, 1885, **18**, 3430 ; Leuchs and co-workers, *ibid.* 1908, **41**, 4393 ; 1909, **42**, 2681 ; 1912, **45**, 3686.

[5] Tafel, *Annalen*, 1898, **301**, 299.

[6] *Trans. Chem. Soc.* 1910, **97**, 309. *Cf.* Oliveri-Mandala and Comella, *Gazzetta,* 1923, **53**, 276, 619.

This formula affords an explanation of the results obtained by Leuchs and collaborators,[1] who found that when strychnine dissolved in acetone is oxidised with permanganate it yields strychninonic acid, $N : C_{17}H_{18}(: N.CO)(CO)(COOH)_2$, which on reduction with sodium amalgam gives the corresponding hydroxydicarboxylic acid, strychninolic acid, $N : C_{17}H_{18}(: N.CO)(CHOH)(COOH)_2$ and this on treatment with dilute potash yields glycollic acid and strychninolone, $C_{19}H_{18}O_3N_2$, which is neutral. The formation of these substances is explained by Perkin and Robinson's formula thus :

Strychninonic acid

Strychninolic acid

Intermediate product
(+ *glycollic acid*)

Strychninolone
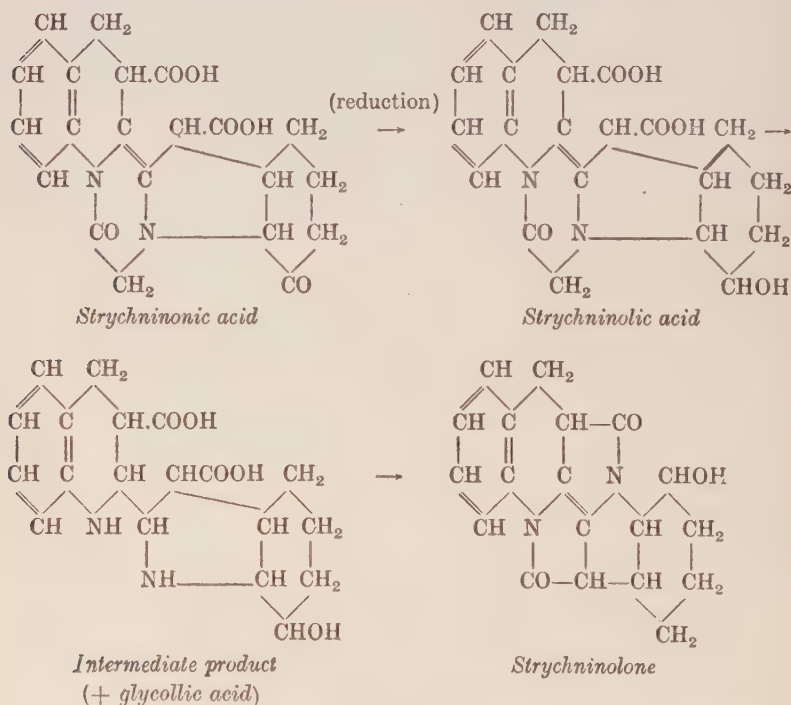
Perkin and Robinson regard *iso*strychnine and *iso*strychninic acid as structural isomerides of strychnine and strychninic acid respectively, the isomerism being due to change of the double bond marked (*a*) to the position marked (*b*) in the formula for strychnine (p. 185), and migration of an H atom from the position marked * to that marked †.

[1] *Berichte*, 1908, **41**, 1711 ; 1909, **42**, 2494 ; 1910, **43**, 2417 ; 1912, **45**, 201. For later developments of this work *see ibid.* 1913, **46**, 3693 ; 1914, **47**, 1552 ; 1915, **48**, 1009 ; 1919, **52**, 1443, 1583 ; 1922, **55**, 3738.

Brucine, $C_{23}H_{26}O_4N_2$. Brucine was first obtained in 1819 by Pelletier and Caventou from *Strychnos Nux-vomica* bark, which was then supposed to be derived from *Brucea ferruginea*. Its composition was determined by Regnault.

Preparation. The mother liquors from strychnine (p. 180) are concentrated and the alkaloids precipitated as neutral oxalates which are dried and extracted with dry alcohol in which the strychnine salt is the more soluble. The less soluble salt is dissolved in water, decolorised with charcoal, the alkaloid regenerated with ammonia, dried and extracted with acetone or dry alcohol in which strychnine is less soluble. The brucine is finally recrystallised from dilute alcohol. Flückiger has stated that if the mixture of the two alkaloids is converted into the acetates and the solution evaporated to dryness, the strychnine salt dissociates into the alkaloid and acetic acid, whilst brucine acetate remains unchanged and may be dissolved out by cold water. A method of separation depending on the greater solubility in water of strychnine hydriodide was successfully employed by Shenstone,[1] whilst others have made use of the sparing solubility of strychnine chromate for the removal of small quantities of this alkaloid from brucine.

Brucine crystallises from water or aqueous alcohol in monoclinic prisms containing $4H_2O$, m.p. 105° or 178° (*dry*), $[\alpha]_D - 119°$ to $127°$ in chloroform. The alkaloid is slightly soluble in cold water (1 in 320) more so in boiling water (1 in 150), very soluble in alcohol, chloroform, or amyl alcohol, almost insoluble in ether.

Brucine is a monoacidic base ; the salts crystallise well and are readily soluble in water. The hydrochloride, $B.HCl$, forms small groups of needles, the hydriodide, $B.HI$, leaflets sparingly soluble in water and the sulphate, $B_2.H_2SO_4.7H_2O$, long needles.

Brucine is easily distinguished from strychnine by not giving the characteristic play of colours when oxidised with chromic acid, and by affording an intense red colour with nitric acid. This red coloration may be distinguished from that given by morphine by cautiously adding stannous chloride, when in the case of brucine the red colour changes to violet.

Constitution. It has long been surmised that brucine is a dimethoxystrychnine, and all the work done on it shows that it yields a series of derivatives, parallel with those obtained in like manner from strychnine, the two series differing by $2CH_2O$, *i.e.*, by the replacement of two hydrogen atoms by two methoxyl groups.

[1] *Journ. Chem. Soc.*, 1881, **39,** 456.

The most important reactions bearing on the constitution of brucine are summarised in the following paragraphs.

When warmed with sodium in alcohol at $80°$ it takes up a molecule of water, forming brucinic acid, $C_{23}H_{28}O_5N_2$ (microscopic needles, m.p. $245°$) which is very unstable, and on heating is reconverted into brucine ; it reacts with nitrous acid to form a nitrosamine and is an iminocarboxylic acid, of which brucine is the betaine, just as strychnine is the betaine of strychninic acid.　Brucine forms a methiodide, which crystallises in needles, m.p. $270°$ (*decomp.*). Brucinic acid methiodide forms small needles, m.p. $218°$, which readily lose water, passing into brucinemethiodide ; the latter on digestion with silver oxide gives methylbrucine.

$$N \ \vdots \ C_{20}H_{20}(OCH_3)_2O—CO \qquad\qquad N \ \vdots \ C_{20}H_{20}(OCH_3)_2O—COOH$$
$$\diagdown | \qquad\qquad\qquad\qquad\qquad \diagdown$$
$$N \qquad\qquad\qquad\qquad\qquad\qquad NH$$

Brucine *Brucinic acid*

$$\lceil \underline{\qquad\qquad\qquad} O \neg$$
$$MeN \ \vdots \ C_{20}H_{20}(OCH_3)_2.O.CO$$
$$\diagdown$$
$$NH$$

Methylbrucine
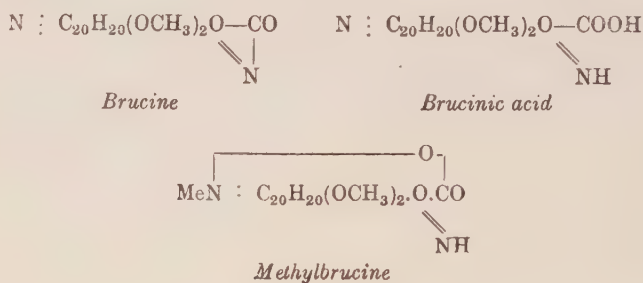
When reduced electrolytically brucine is converted into tetrahydrobrucine, $C_{23}H_{30}O_4N_2$, and brucidine, $C_{23}H_{28}O_3N_2$, analogous with tetrahydrostrychnine and strychnidine.[1]

$$N \ \vdots \ C_{20}H_{20}(OCH_3)_2O—CH_2OH \qquad N \ \vdots \ C_{20}H_{20}(OCH_3)_2O—CH_2$$
$$\diagdown \qquad\qquad\qquad\qquad\qquad\qquad \diagdown |$$
$$NH \qquad\qquad\qquad\qquad\qquad\qquad N$$

Tetrahydrobrucine *Brucidine*
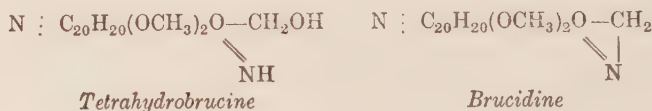
On oxidation with permanganate in acetone solution brucine furnishes bruciconic acid, $N \vdots C_{17}H_{16}(OCH_3)_2(\vdots N.CO)(CO)(COOH)_2$, and this on reduction yields the corresponding hydroxydicarboxylic acid, brucinolic acid, $N \vdots C_{17}H_{16}(OCH_3)_2(\vdots N.CO)(CHOH)(COOH)_2$, which by hydrolysis, (1) with dilute potash furnishes brucinolone $C_{21}H_{22}O_5N_2$, and (2) (as the acetyl derivative) with hydrochloric acid yields curbine, $C_{18}H_{20}O_5N_2$, with malonic acid as a by-product. The first three substances correspond to strychninonic acid, strychninolic acid, and strychninolone respectively (*see* p. 186), and have

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[1] Tafel and Naumann, *Berichte*, 1901, **34,** 3291.

been fully investigated by Leuchs and collaborators, and shown to contain the two methoxyl groups of the parent base.[1]

On oxidation with chromic acid brucine yields Hanssen's acid, $C_{15}H_{17}O_2N_2.COOH$, identical with that furnished by strychnine (*see* p. 185), so that in this oxidation the ring containing the two methoxyl groups of brucine must have disappeared. Perkin and Robinson,[2] after elaborating their formula for strychnine, pointed out that the positions of the two methoxyl groups in brucine are fairly clearly fixed by this fact, and by the observation of Leuchs and Weber [3] that brucinolone on treatment with dilute nitric acid yields a quinone, $C_{19}H_{16}O_5N_2$, crystallising in red needles, m.p. 295°, and which is reduced by sulphurous acid to the corresponding quinol-bisdesmethylbrucinolone, $C_{19}H_{18}O_5N_2$. A similar quinone (cacotheline) is formed when brucine is treated with nitric acid, and is the cause of the well-known brucine reaction with nitric acid.[4]

These quinones have all the properties of *p*-quinones, and consequently Perkin and Robinson suggest that brucine may be represented as a dimethoxystrychnine of the following formula:
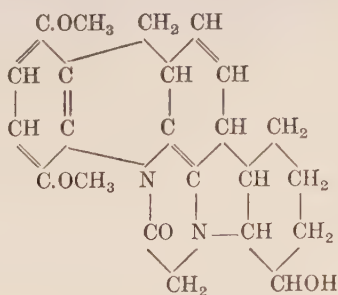
Brucine (Perkin and Robinson)

Struxine, $C_{21}H_{30}O_4N_2$, obtained by Schaefer from deteriorated nux-vomica seeds in about 0·1 per cent. yield, is regarded as a decomposition product of brucine or strychnine and was obtained as the sulphate by just neutralising a solution in dilute sulphuric

[1] *Berichte*, 1908, **41**, 1711 ; 1909, **42**, 770 ; 1912, **45**, 201, 2653, 3412 ; 1913, **46**, 3917.

[2] *Trans. Chem. Soc.* 1910, **97**, 309.

[3] *Berichte*, 1909, **42**, 3709.

[4] Leuchs and collaborators, *ibid.* 1911, **44**, 2136, 3040. For later developments of this work *see ibid.* 1918, **51**, 1375 ; 1919, **52**, 2195, 2204 ; 1921, **54**, 2177 ; 1922, **55**, 564, 724, 1244, 2403, 3729, 3936 ; 1923, **56**, 502, 1775, 1780, 2472.

acid of the total alkaloids. It is crystalline and yields crystalline salts (normal and acid), and is only slightly bitter.[1]

Strychnicine. This alkaloid, isolated by van Boorsma from the leaves of *Strychnos Nux-vomica*, grown in Java, forms colourless needles, which begin to decompose at 240°. It is characterised chiefly by the fact that when a solution of sodium hydroxide is added drop by drop to a solution of a salt of the alkaloid in water, a precipitate is formed, which with more alkali redissolves, forming an orange-tinted liquid, which develops a deep violet colour on farther addition of hydrochloric acid. Strychnicine is scarcely poisonous, though it causes tetanus in frogs.[2]

Physiological Action of Strychnos Alkaloids. Brucine closely resembles strychnine in physiological action, but is less poisonous, the relative toxicities of the two alkaloids being as 4 : 33. It also differs from strychnine in its more marked curare-like action on the nerve terminations in voluntary muscle. Strychnine is highly toxic ; in poisonous doses it acts principally on the spinal cord, causing excessive reflex irritability, which results in convulsions (tetanus) in which all the muscles of the body are involved. The respiratory muscles are affected in the paroxysm, and, as a general rule, after two or three convulsions respiration fails to return. With very large doses death may occur almost immediately from asphyxia resulting from paralysis of. the central nervous system. The terminations of the motor nerves are paralysed by large doses of strychnine in the same way as by curare, but this effect is only well seen in certain kinds of frogs where this action occurs before that on the central nervous system. In small quantities strychnine slows the heart and raises the blood-pressure, and, with poisonous doses, the blood-pressure is very high, due to the increased activity of the vaso-motor centre.

In medicine strychnine is chiefly used as a " tonic " for the sake of its local action on the digestive organs. It is also employed in various forms of paralysis owing to its stimulant action on the central nervous system. It has been used as a remedy in chronic alcoholism. Its principal use is probably as a vermin killer.

Among the other tetanising alkaloids are the doubtful " cala-barine " and gelsemine. Thebaine, belonging to the opium group, is more active than brucine, but much less so than strychnine in

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[1] *Journ. Amer. Pharm. Assoc.* 1914 [i], 677 (*Chem. Soc. Abstr.* 1915 [i], 86).

[2] *Bull. Inst. bot. Buitenzorg,* 1902, No. XIV. p. 3.

producing tetanus. It has been supposed that the tetanising action of strychnine is correlated with the existence of the keto-di-nitrogen

group

$$
\begin{array}{c}
\text{C---} \\
\diagup\,\diagdown\!\diagdown \\
\text{---N}\quad\text{C---} \\
|\qquad| \\
\text{CO}\quad\text{N---} \\
\diagdown\,\diagup \\
\text{CH}_2
\end{array}
$$
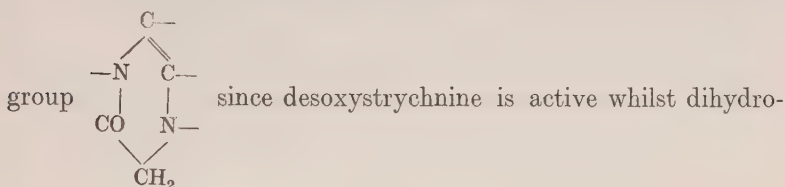
since desoxystrychnine is active whilst dihydro-

strychnoline and strychnoline, in which the : CO group has become : CH_2, are not.[1]   But against this view is the fact that strychnidine, which contains : CH_2 in place of : CO, lies between desoxystrychnine and strychnine as a tetanising poison, whilst strychninonic acid (p. 186), which contains the keto-di-nitrogen ring intact, is non-poisonous.[2]

Strychnine oxide, $C_{21}H_{22}O_3N_2.3H_2O$, m.p. $216°–217°$ (dry), $[\alpha]_D^{21} - 1.75°$, obtained by Pictet and Mattisson [3] by the action of hydrogen peroxide on strychnine is said to be about as toxic as strychnine itself, whilst isostrychnine $(see$ p. 186) is about as toxic as brucine.

ALKALOIDS OF CURARE

Curare consists of a highly toxic dried aqueous extract of various species of *Strychnos* indigenous to South America, where it is prepared by Indians for use as an arrow poison. It was first examined by Roulin and Boussingault in 1829, who isolated from it a crystalline alkaloid curarine ; some years later a similar alkaloid was obtained by Buchner, and in 1865 Preyer announced that he had obtained curarine and its salts in a well-crystallised condition, and by analysis of the platinichloride ascertained its composition to be $C_{10}H_{35}N$. In 1878 curare was reinvestigated by Sachs,[4] who was only able to obtain an amorphous alkaloid, to which he assigned the empirical formula, $C_{18}H_{35}N$.   The more recent work of Boehm [5] to a certain extent explains these discrepant results, since he shows that the curare of commerce varies in composition.   According to this author the extract is of three kinds, distinguished by the packing in which they are sent into commerce : (a) *Para curare*, in

[1] Perkin and Robinson, *Trans. Chem. Soc.* 1910, **97,** 318.

[2] *Cf.* Loeb and Oldenburg, *Abstr. Chem. Soc.* 1912 [ii], 373 ; and Paderi, *ibid.* 1915 [i], 750.

[3] *Berichte*, 1905, **38,** 2782.   *Cf.* Mossler, *Monats.* 1910, **31,** 329.

[4] *Annalen*, 1878, **191,** 354.

[5] *Arch. Pharm.* 1897, **235,** 660 ; and *Pfluger's Archiv.* 1910, **136,** 203.

bamboo tubes ; (*b*) *Calabash curare*, in gourds ; (*c*) *Pot curare*, in unburnt earthenware pots. The drug contains alkaloids of two kinds, typified by the curine and curarine of Para curare, the former having a paralysing action on the heart, the latter exhibiting the paralysing action on nerve endings, characteristic of curare.

Para Curare. This is the variety now found in commerce. It consists of a dark brown extract containing much quercitol. The toxic dose for rabbits is 0·005 to 0·01 grm. per kilogram of body weight. It contains the alkaloid, CURINE, $C_{18}H_{19}O_3N$, to the extent of 12 to 15 per cent. This is isolated by extracting with water, precipitating with ammonia solution, and recrystallising the precipitated alkaloid from benzene, when it forms four-sided prisms, m.p. 161°, containing 1 mol. of benzene, m.p. 212° (*dry*). It is soluble in aqueous alcohol or dilute acids, but insoluble in water, is precipitated by *meta*phosphoric acid, and with sulphovanadic acid gives a black solution, which becomes dark blue and eventually bright red. The platinichloride is an amorphous yellow powder : the methiodide forms yellow needles, m.p. 252°, and the metho-chloride, rhombic plates. The alkaloid contains a methoxyl, but no hydroxyl group. Since on distillation with zinc dust it gives a substance having the properties of *para*quinoneanisole, Boehm considers that curine contains a methylquinoline nucleus. In addition to this crystalline alkaloid, Boehm obtained from the mother liquor an amorphous, bitter, highly toxic base, soluble in water or alcohol, and having the characteristic physiological action of curare. This was named PARACURARINE or TUBOCURARINE $C_{19}H_{21}O_4N$.[1]

Calabash Curare. This extract was formerly well known in commerce and was probably prepared from *Strychnos toxifera*. The toxic constituent is apparently an amorphous CURARINE, $C_{19}H_{26}ON_2$ yielding a crystalline hydrochloride.

Pot Curare is a dark brown, comparatively dry, extract obtained principally from *Strychnos Castelnæi*. It contains PROTOCURINE $C_{20}H_{23}O_3N$, which crystallises from methyl alcohol in colourless needles, m.p. 306° (*decomp.*). Its salts crystallise well and are bitter to the taste. This base is slightly toxic. A similar base PROTOCURIDINE, $C_{19}H_{21}O_3N$, crystallises from boiling chloroform in prisms, m.p. 274°–276°, and is not toxic. The poisonous constituent is PROTOCURARINE, $C_{19}H_{23}O_2N$, an amorphous red powder easily soluble in water, and giving characteristic colour reactions with

[1] *Cf.* Buraczewski and Zjibewski, *Bull. Acad. Sci. Crac.* 1910, 352.

sulphuric and nitric acids. It is intensely poisonous, the toxic dose for rabbits being 0·00024 grm. per kilogramme of body weight.

Physiological Action of Curare. Curare, unlike strychnine and brucine, exerts a strong paralysing action on the motor nerve endings supplying striated muscle, without affecting the excitability of muscle. This action appears to be due to the *curarines*, none of which have yet been obtained in a pure state.[1]

Strychnos Vacacoua

Bakankosine, $C_{16}H_{23}O_8N.H_2O$, was isolated by Bourquelot and Hérissey [2] from the seeds of *Strychnos Vacacoua*, Baill., and is described as a nitrogenous glucoside. It forms large colourless crystals from alcohol, melts at 157°, remelts at 200°, and has $[\alpha]_D$ — 205·2°. It is hydrolysed by boiling dilute acids and by emulsin, yielding dextrose and a product, $C_{10}H_{13}O_3N$. Neither bakankosine nor its hydrolytic product is toxic.

ALKALOIDS OF *ECHINOPS SPP*

From *Echinops Ritro* (seeds) and other species of Echinops, Greshoff [3] isolated an alkaloid, which he named ECHINOPSINE, but which Späth and Kolbe [4] have shown recently is identical with 1-methyl-4-quinolone, $C_{10}H_9ON$, already prepared in an impure condition by Meyer.[5]

In addition to this substance, Greshoff obtained from the same source β-ECHINOPSINE, m.p. 135°, and ECHINOPSEINE.

[1] *Cf.* Edmund and Roth, *Amer. J. Physiol.* 1908, **23,** 28, 46.
[2] *Compt. rend.* 1907, **144,** 575 ; 1908, **147,** 750.
[3] *Rec. trav. Chim.* 1900, **19,** 360.
[4] *Monats.* 1923, **43,** 469.
[5] *Ibid.* 1906, **27,** 255.

V. ISOQUINOLINE GROUP

ANHALONIUM ALKALOIDS

A NUMBER of plants known by the name " pellote," and belonging to the genus *Anhalonium* (*Mammillaria*) are used by Mexican Indians to produce intoxication in the course of certain religious ceremonies. The best-known product of this kind is the flowering heads of *Anhalonium Lewinii*, which have been imported into Europe for use in medicine under the name " mescal buttons." The following alkaloids of this group are known : [1]

Hordenine (Anhaline), $C_{10}H_{15}ON$, in *A. fissuratum*, see p. 347.

Anhalamine, $C_{11}H_{15}O_3N$, in *A. Lewinii*.

Mezcaline, $C_{11}H_{17}O_3N$, in *A. Lewinii*.

Anhalonidine, $C_{12}H_{17}O_3N$, in *A. Lewinii*.

Anhalonine, $C_{12}H_{15}O_3N$, in *A. Lewinii* and *A. Jourdanianum*.

Lophophorine, $C_{13}H_{17}O_3N$, in *A. Lewinii*.

Pellotine, $C_{13}H_{19}O_3N$, in *A. Lewinii* and *A. Williamsii*.

The alkaloids present in " mescal buttons " may be isolated by the following process : [2] The ground heads are exhausted with alcohol, the extract concentrated to a small bulk and set aside to deposit resin. To the clear liquor, ammonia solution is added in excess, and the alkaloids extracted with chloroform. The chloroform solution is in turn extracted with dilute sulphuric acid, from which anhalonine, lophophorine, and pellotine, are removed by adding ammonia and shaking with ether. The remaining alkaloids, anhalamine, anhalonidine, and mezcaline, are then taken out by means of chloroform. The ether-soluble alkaloids are converted into the mixed hydrochlorides, which on recrystallisation from dry alcohol separate in the order anhalonine, pellotine, lophophorine. The second group of alkaloids, viz., those sparingly soluble or insoluble in ether, are converted into the sulphates ; these on solution in hot water deposit some mezcaline sulphate on cooling. The mother liquors are treated with ammonia and shaken out with

[1] *Cf.* Lewin, *Arch. f. exp. Path.* 1888, **24**, 401 ; 1894, **34**, 374. Heffter, *ibid.* 1894, **34**, 82 ; 1898, **40**, 385 ; *Berichte*, 1894, **27**, 2975 ; 1896, **29** 216 ; 1898, **31**, 1193. Ewell, *Journ. Amer. Chem. Soc.* 1896, **18**, 624.

[2] Kauder, *Arch. Pharm.* 1899, **237**, 190.

chloroform, when anhalamine remains undissolved. The alkaloids passing into solution, mezcaline and anhalonidine, are separated by conversion into the hydrochlorides, and treatment of these with hot alcohol, in which anhalonidine hydrochloride is insoluble, whilst the mezcaline salt dissolves. According to Heffter,[1] mescal buttons contain mezcaline 6·3 per cent., anhalonidine 5·3 per cent., anhalonine 3 per cent., and lophophorine 0·5 per cent.

Hordenine, $C_{10}H_{15}ON$ (*Anhaline*) (see p. 347), was isolated by Heffter[2] from *A. fissuratum* and named anhaline, and later shown by Späth to be hordenine.[3]

Anhalamine, $C_{11}H_{15}O_3N$, microscopic needles, m.p. 185·5°, $[\alpha]_D$ 0°, dissolves in boiling chloroform or benzene. The hydrochloride, $B.HCl.2H_2O$, forms lustrous leaflets from water, and the sulphate, $B_2.H_2SO_4$, colourless prisms. The base contains two methoxyl groups and one hydroxyl group. Both a dibenzoyl derivative, m.p. 128°–129°, and a monobenzoyl derivative, m.p. 167·5°, are formed, the latter, but not the former, being soluble in alkalis.

Mezcaline, $C_{11}H_{17}O_3N$, is a colourless alkaline oil, b.p. 180°–180·5°/12 mm., which absorbs carbon dioxide from the air, forming a crystalline carbonate. It is soluble in chloroform, benzene, alcohol or water, but insoluble in dry ether or light petroleum. The sulphate, $B_2.H_2SO_4.2H_2O$, forms brilliant prisms, m.p. 183°–186°, the hydrochloride colourless crystals, picrate, m.p. 216°–218°, and the platinichloride $(B.HCl)_2.PtCl_4$, bright yellow needles, m.p. 187°–188°. The alkaloid contains three methoxyl groups and behaves as if it contained the grouping, .NHMe. The methiodide, $B.CH_3I$, crystallises in colourless prisms, m.p. 169°, and on shaking with chloroform furnishes methylmezcaline ; the methiodide of the latter crystallises in pale yellow plates, m.p. 224°–225°. Benzoylmezcaline forms lustrous needles, m.p. 120°. On oxidation mezcaline yields 3 : 4 : 5-trimethoxybenzoic acid and a small amount of a neutral nitrogenous substance.

The alkaloid gives a lemon-yellow coloration with sulphuric acid, passing into violet on warming or on adding a small fragment of sucrose or sodium nitrate. A similar reaction is given by all the alkaloids of this group.

Anhalonidine, $C_{12}H_{17}O_3N$, crystallises in small octahedra, m.p. 154°, $[\alpha]_D$ 0°, and dissolves readily in chloroform, alcohol, or

[1] *Berichte,* 1896, **29,** 216.
[2] *Ibid.* 1894, **27,** 2976.
[3] *Monats.* 1919, **40,** 129.

water, but is insoluble in light petroleum and nearly so in dry ether. The aqueous solution is strongly alkaline. The hydrochloride, B.HCl, crystallises in prisms, but the platinum and gold salts are amorphous. The alkaloid contains two methoxyl groups. Benzoyl-anhalonidine crystallises in lustrous plates, m.p. 189°. With methyl iodide the alkaloid forms methylanhalonidine hydriodide (yellow prisms, m.p. 125°–130°).

Anhalonine, $C_{12}H_{15}O_3N$, crystallises from light petroleum in long needles which melt at 85°. It is soluble in water, alcohol, or ether ; the solutions are lævorotatory. The hydrochloride, B.HCl, forms colourless prisms ; the platinichloride, $(B.HCl)_2.PtCl_4$, golden-yellow needles. Anhalonine contains one methoxyl group. It is a secondary base, forms a nitroso derivative, and reacts with methyl iodide, forming a N-methylanhalonine, which in turn gives a methiodide, $C_{12}H_{14}O_3N(CH_3).CH_3I$, m.p. 210°.

Lophophorine, $C_{13}H_{17}O_3N$, is a colourless syrup, insoluble in water, but readily soluble in organic solvents. The hydrochloride, B.HCl, crystallises in small colourless needles. The base contains one methoxyl group. It is isomeric, but not identical with methyl-anhalonine.

Pellotine, $C_{13}H_{19}O_3N$, occurs in *A. Williamsii* (*Echinocactus Williamsii*) to the extent of 3·5 per cent.[1] It was found in *A. Lewinii* by Kauder,[2] but this may have been due to the presence of *A. Williamsii* heads in the plant material used. It crystallises from alcohol in transparent tablets, m.p. 110°. The hydrochloride, B.HCl, forms rhombic prisms. The alkaloid contains two methoxyl groups, a methylimino group and a phenolic hydroxyl group. The methiodide, $B.CH_3I.H_2O$, crystallises in small prisms, m.p. 198°. When distilled with soda-lime, trimethylamine is formed.

Constitution of the Anhalonium Alkaloids. From Heffter's results it was possible to extend the formulæ assigned to six out of the seven anhalonium alkaloids as follows :

Anhaline, $C_{10}H_{15}ON$ (since identified with hordenine).
Anhalamine, $C_9H_7(OMe)_2(OH) : NH$.
Mezcaline, $C_6H_2(OMe)_3(CH_2.NHMe)$ (3 : 4 : 5 : 1).
Anhalonidine, $C_{10}H_9(OMe)_2(OH) : NH$.
Anhalonine, $C_{11}H_{13}O_2(OMe) : NH$.
Lophophorine, $C_{12}H_{14}O_2N(OMe)$.
Pellotine, $C_{10}H_9(OMe)_2(OH).NMe$.

[1] Heffter, *Monats.* 1894, **27**, 2975 ; 1901, **34**, 3004.
[2] *Arch. Pharm.* 1899, **237**, 190.

Heffter proved that mezcaline was not identical with the base having the formula shown above, which he synthesised for this purpose, [1] and it was not until 1919 when Späth began his work on these alkaloids, that their relationships were cleared up. In his first paper [2] this author stated that anhaline was identical with hordenine (β-p-hydroxyphenylethyldimethylamine, $HO.C_6H_4.CH_2. CH_2.NMe_2$, p. 347), and described the synthesis of mezcaline by the following series of reactions.   Galloyl chloride (3 : 4 : 5-trimethoxy-benzoyl chloride) was reduced by Rosenmund's method [3] to 3 : 4 : 5-trimethoxybenzaldehyde, which was condensed with nitromethane to ω-nitro : 3 : 4 : 5-trimethoxystyrene, $C_6H_2.(OMe)_3.CH : CH.NO_2$. This on reduction with zinc dust and acetic acid yielded the corresponding oxime, which was further reduced by sodium amalgam to β-3 : 4 : 5-trimethoxyphenylethylamine, $C_6H_2(OMe)_3.CH_2.CH_2.NH_2$ and this proved to be identical with mezcaline.   Like the latter, it behaves as if it contained the grouping --NHMe, apparently due to a rearrangement occurring in presence of methyl iodide or benzoyl chloride.

When mezcaline is condensed with formaldehyde it yields 6 : 7 : 8-trimethoxy-1 : 2 : 3 : 4-tetrahydro*iso*quinoline   and   the quaternary iodide obtained from this is identical with dimethyl-anhalamine methiodide, [4] whence it follows that O-methylanhalamine must be 6 : 7 : 8-trimethoxy-1 : 2 : 3 : 4-tetrahydro*iso*quinoline.

The free hydroxyl group in anhalamine was subsequently shown to occupy position 6 by the synthesis of this alkaloid from 5 : hydroxy-3 : 4-dimethoxybenzaldehyde by methods analogous with those just described, the hydroxyl group being protected up to the last stage by benzylation. [5]

The N-acetyl derivative of mezcaline, $C_6H_2(OMe)_3.CH_2.CH_2. NHAc$, on treatment with phosphoric oxide, yields 6 : 7 : 8-tri-methoxy-1-methyl-3 : 4-dihydro*iso*quinoline, which on catalytic hydrogenation adds on two further hydrogen atoms at positions 1 : 2, and this product yields, with methyl sulphate, 6 : 7 : 8-trimethoxy-1 : 2-dimethyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline, which is identical with methylpellotine, whence it appears that pellotine must be a dimethyl ether of 6 : 7 : 8-trihydroxy-1 : 2-dimethyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline.   Pellotine and anhalonidine on complete

[1] *Berichte*, 1901, **34**, 3004 (with Capellmann, 1905, **38**, 3634).
[2] *Monats.* 1919, **40**, 129 ; 1921, **42**, 263.
[3] *Berichte*, 1918, **51**, 585.
[4] Späth, *Monats.* 1922, **42**, 97.
[5] Späth and Röder, *ibid.* 1922, **43**, 93.

methylation yield the same product, and as anhalonidine is a secondary base and differs from pellotine by containing $.CH_2$ less it must be a dimethyl ether of 6 : 7 : 8-trihydroxy-1-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline,[1] and pellotine should be *N*-methylanhalonidine.

The position of the free hydroxyl group in these two alkaloids is either 6 or 8, since Späth has shown that the *O-N*-diacetyl derivative of β-5-hydroxy-3 : 4-dimethoxyphenylethylamine when heated in toluene solution with phosphoric oxide yields a product which must be either 6-acetoxy-7 : 8-dimethoxy or 8-acetoxy-6 : 7-dimethoxy-1-methyl-3 : 4-dihydro*iso*quinoline. On reduction with tin and hydrochloric acid it is converted into anhalonidine, which must, therefore, be 6- or 8-hydroxy-7 : 8 or 6 : 7-dimethoxy-1-methyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline. Similarly, the methiodide of the acetoxy compound on reduction yields, by loss of acetic acid and addition of two hydrogen atoms, pellotine, proving the latter to be *N*-methylanhalonidine.[2] The relationships of these five anhalonium alkaloids may be illustrated by the following formulæ :

Bordenine   *Mezcaline*   *Anhalamine*
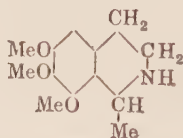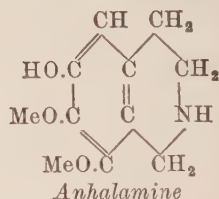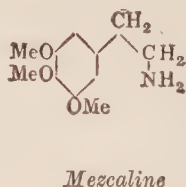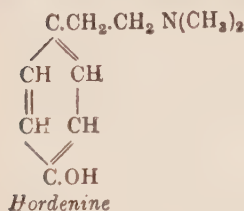
Anhalonidine O-methyl ether [3]   *Pellotine O-methyl ether* [3]
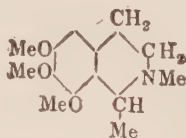
Quite recently Späth and Gangl [4] have synthesised anhalonine and shown it to be 6-methoxy-7 : 8-methylenedioxy-1-methyl-tetrahydro*iso*quinoline, the quaternary iodide of which is lophophorine methiodide.

Physiological Action of Anhalonium Alkaloids. Dixon has shown [5] that the physiological action of anhalonidine, anhalonine

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[1] Späth, *Monats.* 1922, **42,** 97.

[2] Späth, *ibid.* 1923, **43,** 477.

[3] In these cases the position of the free hydroxyl in the original alkaloids is still unsettled, but is either — 6 or — 8.

[4] *Monats.* 1923, **44,** 103 (*Chem. Soc. Abstr.* 1924 [**i**], 69).

[5] *Journ. Physiol.* 1899, **25,** 66.

lophophorine, and mezcaline is qualitatively the same. They cause an increased flow of saliva, occasionally vomiting, and in large doses diarrhœa. The action of the heart is slowed and there is a fall in blood-pressure. With toxic doses respiration becomes quicker and shallower, and death results from failure of the respiratory centre. In animals there is at first increased reflex activity, then paralysis, which is central in origin.

In man there is a preliminary stage of excitement, resembling that produced by alcohol. A number of subjective sensations are also experienced ; a feeling of " dual existence " and increased sensitiveness to colours and to music are noticed, and a kaleidoscopic play of colours is seen. The alkaloids are excreted in the urine and there is some diuresis. Lophophorine is the most powerful of the alkaloids, but mezcaline is most active in producing colour vision.

The following additional observations are mainly due to Lewin and Heffter : The physiological action of anhalamine has not been investigated. Anhaline (hordenine) exercises a paralysing action on the central nervous system. Anhalonine is toxic, producing reflex irritability in small doses and reflex tetanus in large doses ; the lethal dose of the hydrochloride for rabbits is 0·16 to 0·2 grm. per kilogramme of body weight. The quaternary ammonium derivatives of anhalonidine show the characteristic physiological action of such products and produce paralysis of the motor nerve endings in frogs, but this is not the case with the corresponding anhalonine derivatives. Lophophorine is the most toxic of this group of alkaloids, 0·011 grm. per kilogramme of body weight being the lethal dose for frogs. Pellotine is slightly narcotic, and has been used in medicine as a hypnotic in doses of one-third to two-thirds of a grain.

ALKALOIDS OF *HYDRASTIS CANADENSIS*
(" GOLDEN SEAL ")

The rhizomes of this plant contain at least three alkaloids, berberine, hydrastine and canadine, of which the second is the chief physiologically active constituent. The rhizomes and roots as found in commerce are generally stated to contain about 1·5 per cent. of hydrastine, and 2·5 per cent. of berberine, but higher percentages of both are frequently recorded.[1]

Preparation. The finely-ground drug is extracted with alcohol

[1] *E.g.* Wasicky and Joachimowitz, *Arch. Pharm.* 1917, **255,** 497.

or water acidified with acetic acid, the extract concentrated to a low bulk and a slight excess of 20 per cent. sulphuric acid added, when berberine sulphate separates on standing, and can be collected and recrystallised from the minimum quantity of water by addition of alcohol and sulphuric acid, as berberine acid sulphate. The filtrate from the crude berberine sulphate on addition of excess of ammonia yields crude hydrastine, which may be purified by reprecipitation from dilute sulphuric acid solution by ammonia and recrystallisation from boiling alcohol [1] or ethyl acetate, [2] and finally from a mixture of chloroform and alcohol. Hydrastine may be prepared more rapidly by extracting the ground rhizome with ether (or benzene) and dissolving the residue left on distilling off the solvent in hot alcohol, when nearly pure hydrastine crystallises out on cooling. [3] From the residual drug berberine may be isolated as described above.

Estimation of Alkaloids in Hydrastis rhizome. The United States Pharmacopœia (9th Rev.) gives the following process : 10 grm. of the rhizome in No. 60 powder are allowed to stand ten minutes with 100 c.c. of ether, and a further two hours after adding 5 c.c. ammonia solution (sp. gr. 0·958 at 25°), the flask containing the mixture being shaken at intervals of ten minutes. Fifteen cubic centimetres of water are added, the flask shaken till the drug coheres, and 50 c.c. of the ethereal extract are poured off into a separating funnel. The alkaloid in this is extracted with weak sulphuric acid, which in turn is rendered alkaline with ammonia and the free alkaloid removed by ether. The ethereal extract is run into a tared beaker, the solvent evaporated, the residue dried at 100° and its weight w (which represents the ether-soluble alkaloid from 5 grm. of drug) noted. The United States Pharmacopœia requires hydrastis rhizome to contain not less than 2·5 per cent. of ether-soluble alkaloids as determined by this method.

A similar process is used in the United States Pharmacopœia for estimating ether-soluble alkaloids in galenical preparations of the drug, but the British Pharmacopœia, 1914, gives the following method for estimating hydrastine in such preparations. Ten cubic centimetres of the liquid extract are placed in a 100 c.c. graduated flask, 20 c.c. of potassium iodide solution (B.P.) diluted with 60 c.c.

[1] Power, *Pharm. Journ.* 1884–85 [iii], **15**, 297.
[2] Schmidt and Wilhelm, *Arch. Pharm.* 1888, **226**, 329.
[3] Freund and Will, *Berichte*, 1886, **19**, 2797. *Cf.* Schmidt, *Amer. Journ. Pharm.* 1919, **91**, 270.

of water added, and the whole made up with water to 100 c.c., shaken for several minutes and filtered. Fifty cubic centimetres of the filtrate are run into a separator, made alkaline with ammonia solution and shaken out three times using 30 c.c., 20 c.c. and 20 c.c. of ether. The mixed ethereal solutions are then evaporated, and the residue dried to constant weight on the water-bath. The extract should contain 2 grammes ($\pm$ 0·1) of hydrastine per 100 c.c.[1]

A method of separately estimating hydrastine and berberine in hydrastis rhizome has been proposed by Gordin and Prescott,[2] depending on (1) the isolation of the hydrastine by extraction with ether and its precipitation as pentaiodide, and (2) extraction of the berberine from the residual drug with alcohol and estimation of this as described on p. 209.

Hydrastine, $C_{21}H_{21}O_6M$. This alkaloid was first isolated by Perrins,[3] and was subsequently investigated by Mahla[4] and Power.[5] The present formula is due to Freund and Will,[6] and van Eykman.[7] Hydrastine forms colourless rhombic prisms, m.p. 132° from alcohol. It has a bitter taste, is alkaline to litmus, almost insoluble in water, easily soluble in chloroform (1 in 14 at 25°) or benzene, and less so in alcohol (1 in 170 at 25°) or ether (1 in 175 at 25°). In chloroform, hydrastine has $[\alpha]_D - 67\cdot8°$, but according to Carr and Reynolds the value in dry alcohol is $- 49\cdot8°$, and in 50 per cent. alcohol $+ 115°$.[8]

The salts with acids are unstable in water, and generally not well crystallised ; the hydrochloride, B.HCl, is a microcrystalline powder, m.p. 116°, obtained by passing hydrogen chloride into a solution of the base in ether ; it is dextrorotatory ; the hydriodide periodide, $B.HI.I_5$, is a dark brown powder ; the platinichloride, $B_2.H_2PtCl_6$, is an amorphous, yellow precipitate, but the picrate, $B.C_6H_2(NO_2)_3OH.H_2O$, forms fine yellow needles. The acid oxalate and acid tartrate, $B.H_2C_4H_4O_6.4H_2O$, can be readily

[1] For other processes *see* van der Haar, *Pharm. Weekblaad*, 1911, **48**, 1302 ; de Waal, *ibid.* 1915, **52**, 1423 ; David, *Chem. Soc. Abstr.* 1915 [ii], 601.

[2] *Arch. Pharm.* 1899, **237**, 439. *Cf.* Gordin, *ibid.* 1901, **239**, 638.

[3] *Pharm. Journ.* 1862 [ii], **3**, 546.

[4] *Silliman's Journ.* 1863, **36**, 57.

[5] *Pharm. Record*, 1884, September 10th ; *Pharm. Journ.* 1884–85 [iii], **15**, 297 ; 1885–86 [iii], **16**, 1092.

[6] *Berichte*, 1887, **20**, 88.

[7] *Rec. Trav. Chim.* 1886, **5**, 291.

[8] *Trans. Chem. Soc.* 1910, **97**, 1334. *Cf.* Freund and Will, *Berichte*, 1886, **19**, 2797.

crystallised from hot water. The alkaloid gives ill-defined metallic derivatives, especially with the alkalis.

Hydrastine when dissolved in sulphuric acid gives with ammonium molybdate an olive-green colour. A solution in dilute sulphuric acid develops a blue fluorescence with an aqueous solution of permanganate (1 in 10). Iodine solution precipitates the characteristic periodide as a dark brown powder.[1]

Constitution of Hydrastine. Hydrastine contains two methoxyl groups, and with alkyl iodides behaves as a tertiary amine. It does not react with hydroxylamine or phenylhydrazine. With oxidising agents it furnishes both pyridine derivatives and aromatic acids.[2]

The first important insight into the inner structure of the base was obtained when Freund and Will [3] showed that with dilute nitric acid it undergoes hydrolytic oxidation yielding opianic acid, $C_6H_2[COH : COOH : OMe : OMe = 1 : 2 : 3 : 4]$, and a new base hydrastinine, $C_{11}H_{13}O_3N$, thus :

$$C_{21}H_{21}O_6N \ + \ H_2O \ + \ O \ = \ C_{10}H_{10}O_5 \ + \ C_{11}H_{13}O_3N$$
$$\text{\textit{Hydrastine}} \qquad\qquad\qquad \text{\textit{Opianic acid} \quad \textit{Hydrastinine}}$$

This reaction is analogous with the similar hydrolytic oxidation of narcotine to opianic acid and cotarnine (*see* p. 281), and hydrastinine is allied to cotarnine in constitution and physiological action and can be prepared from it.

HYDRASTININE, $C_{11}H_{13}O_3N$, crystallises from light petroleum in colourless, glancing needles, $[\alpha]_D = 0°$, m.p. 116°–117°, is soluble without colour in non-ionising organic solvents, but dissolves in alcohol and sparingly in water, yielding fluorescent yellow solutions.

It forms salts with the mineral acids, losing at the same time a molecule of water. The hydrochloride, $C_{11}H_{11}O_2N.HCl$, the salt used in medicine, occurs in pale yellowish needles, has a bitter taste, melts at 212°, is very soluble in water or alcohol (1 in 286 of chloroform, or 1 in 300 of ether at 25°. Its aqueous solution shows a blue fluorescence, especially when dilute, is neutral to litmus, and is not precipitated by ammonia solution, but dilute sodium hydroxide solution added drop by drop causes turbidity, which disappears on shaking. On standing, this liquid then deposits crystalline hydrastinine. Bromine water gives, with an aqueous solution of

[1] *Cf.* Lyons, *Pharm. Journ.* 1885–86 [iii], **16**, 880. *Cf.* Mayrhofer, *Chem. Soc. Abstr.* 1915 [ii], 601.

[2] Power, *loc. cit.*

[3] *Berichte*, 1887, **20**, 88.

the salt, a yellow precipitate, which is soluble in ammonia solution.[1]
The hydriodide has m.p. 233°–234°.

Hydrastinine contains a methyl group linked to nitrogen ; [2] it
reacts with hydroxylamine forming an oxime, m.p. 145°–146°, and
with acetic anhydride and benzoyl chloride forming acetylhydrasti-
nine and benzoylhydrastinine respectively. When treated with
caustic alkali it yields *oxyhydrastinine*, $C_{11}H_{11}O_3N$, rosettes of
needles, m.p. 97°–98°, b.p. above 350°, and *hydrohydrastinine*,
$C_{11}H_{13}O_2N$, m.p. 66°.[3] It has already been mentioned that in
forming salts the base loses the elements of a molecule of water.
These reactions indicate that hydrastinine (1) is a secondary amine,
(2) contains an aldehyde group, and (3) contains two side-chains
from which water is readily eliminated on addition of an acid. To
explain these reactions, Roser [4] formulated hydrastinine and its
salts, thus :

$$C_7H_4O_2\begin{cases}CHO\\CH_2.CH_2.NH.CH_3\end{cases} \xrightarrow{+\ HCl} C_7H_4O_2\begin{cases}CH:N(CH_3)Cl\\ \ \ |\\CH_2.CH_2\end{cases}$$

Hydrastinine   *Hydrastinine hydrochloride*
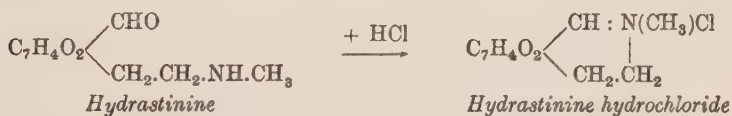
Its conversion into oxyhydrastinine and hydrohydrastinine by
the action of potassium hydroxide recalls the similar conversion of
aromatic aldehydes into a mixture of the corresponding aromatic
alcohol and acid. This change may, therefore, be represented thus :

$$C_7H_4O_2\begin{cases}CH_2OH\\CH_2.CH_2.NH.CH_3\end{cases} \quad (\text{I})$$

$$C_7H_4O_2\begin{cases}CHO\\CH_2.CH_2.NH.CH_3\end{cases}$$

$$C_7H_4O_2\begin{cases}COOH\\CH_2.CH_2.NH.CH_3\end{cases} \quad (\text{II})$$

Hydrastinine   *Intermediate products*
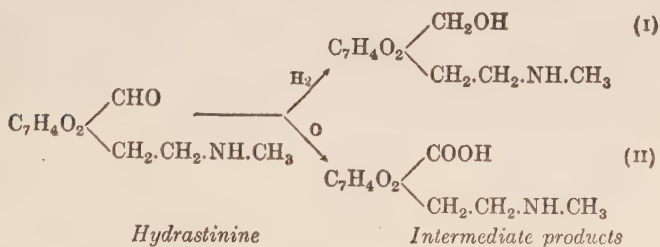
Product I by loss of water forms hydrohydrastinine, and pro-
duct II in like manner, oxyhydrastinine :

$$C_7H_4O_2\begin{cases}CH_2.NCH_3\\ \ \ \ \ |\\CH_2.CH_2\end{cases} \qquad C_7H_4O_2\begin{cases}CO.N.CH_3\\ \ \ \ \ |\\CH_2.CH_2\end{cases}$$

Hydrohydrastinine   *Oxyhydrastinine*
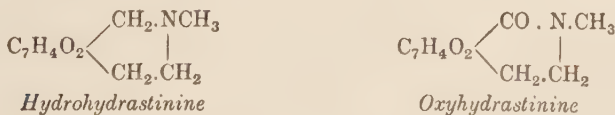
[1] *See also* Reichard, *Pharm. Zentr.-h.* 1911, **52**, 1253.
[2] Herzig and Mayer, *Monats.* 1897, **18**, 379.
[3] Freund and Will, *Berichte*, 1887, **20**, 88, 2400.
[4] *Annalen*, 1888, **249**, 172. *Cf.* Freund, *Berichte*, 1889, **22**, 2329.

Alkaline permanganate converts oxyhydrastinine into hydrastinic acid, $C_{11}H_9O_6N$: this in turn is oxidised by dilute nitric acid to hydrastic acid methylimide, which when warmed with potassium hydroxide furnishes methylamine and hydrastic acid, $C_9H_6O_6$.

$$C_7H_4O_2 \Big\langle {}^{CO.N.CH_3}_{CH_2.CH_2} \longrightarrow C_7H_4O_2 \Big\langle {}^{CO.NH.CH_3}_{CO.COOH} \longrightarrow$$

Oxyhydrastinine　　　　　　　*Hydrastinic acid*

$$C_7H_4O_2 \Big\langle {}^{CO}_{CO} \Big\rangle N.Me \longrightarrow C_7H_4O_2 \Big\langle {}^{COOH}_{COOH}$$

Hydrastic acid methylimide　　　　*Hydrastic acid*
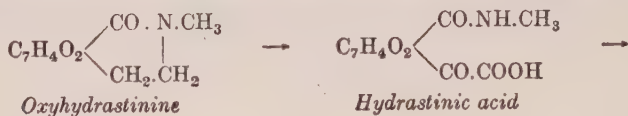
Hydrastic acid also results from exhaustive methylation of hydrastinine, which, as a secondary amine, gives with methyl iodide a mixture of hydrastinine hydriodide and methylhydrastinine methiodide.[1] The latter on distillation with alkali yields trimethylamine and an aldehyde, hydrastal, $C_{10}H_8O_3$, and this on oxidation furnishes hydrastic acid, $C_9H_6O_6$ [1] needles, m.p. 175°, a

$$C_7H_4O_2 \Big\langle {}^{CHO}_{CH_2.CH_2.N(CH_3)_3I} \longrightarrow C_7H_4O_2 \Big\langle {}^{CHO}_{CH:CH_2} \longrightarrow C_7H_4O_2 \Big\langle {}^{COOH}_{COOH}$$

Methylhydrastinine methiodide　　*Hydrastal*　　　*Hydrastic acid*
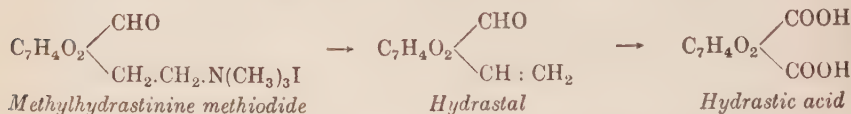
dibasic acid, which on melting passes into an anhydride, and when fused with potassium hydroxide furnishes a mixture of protocatechuic acid and catechol. On heating with strong nitric acid the methylene ether of dinitrocatechol is formed, whilst phosphorus pentachloride converts it into nor*meta*hemipinic acid. These observations show that hydrastic acid is 4 : 5-dioxymethylenephthalic acid. With these data the formulæ for the intervening products back to hydrastinine may be written as follows :

Hydrastic acid　　　*Hydrastic acid methylimide*　　　*Hydrastinic acid*
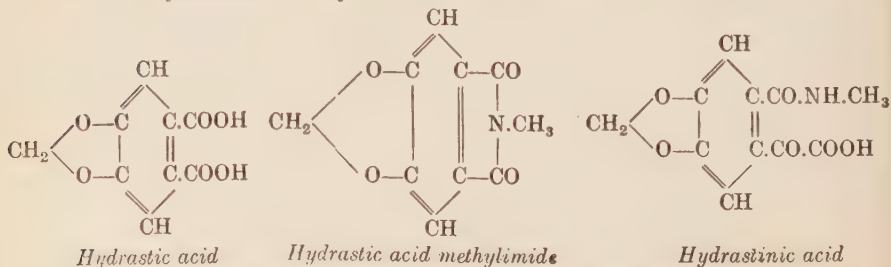
[1] Freund and collaborators, *Berichte*, 1889, **22**, 456, 1156, 2322, 2329 ; *Annalen*, 1892, **271**, 320.
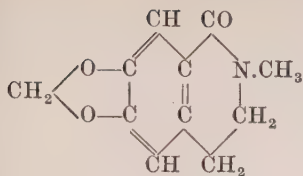
Oxyhydrastinine
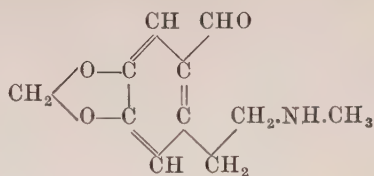
Hydrastinine (Roser)
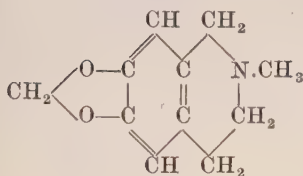
Hydrohydrastinine
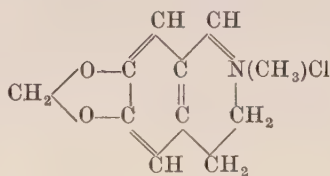
Hydrastinine chloride

This formula for hydrastinine was first confirmed by Fritsch's synthesis [1] of this base by condensing piperonal (4 : 5-dioxymethylenebenzaldehyde) with aminoacetal, $NH_2.CH_2.CH(OC_2H_5)_2$. and treating the piperonylideneaminoacetal so produced with sulphuric acid, thereby converting it into methylenedioxy*iso*quinoline, the methiodide of which on reduction furnished hydrohydrastinine hydriodide ; from this hydrastinine is obtainable by oxidation with chromic acid [2] or iodine in presence of potassium acetate. [3] The various steps in this synthesis may be graphically represented thus :
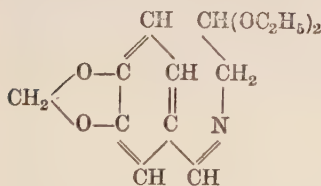
Piperonylideneaminoacetal
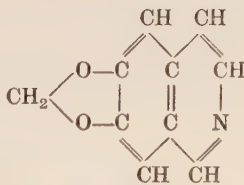
*Methylenedioxyiso*quinoline
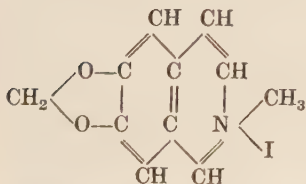
Methylenedioxyisoquinoline methiodide
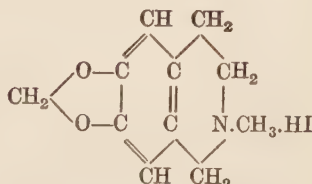
Hydrohydrastinine hydriodide

[1] *Annalen*, 1895, **286**, 18.
[2] Freund, *Berichte*, 1887, **20**, 2403.
[3] German Patent 267,272 (*Chem. Soc. Abstr.* 1914 [i], 79).

Dobbie and Tinkler [1] have suggested that since hydrastinine in solution in ether or chloroform has an absorption spectrum almost identical with that of hydrohydrastinine, whilst the absorption spectra of its solutions in water or alcohol resemble those of the salts, it may exist in two forms represented by formula I (solid state or dissolved in ether or chloroform), and II (dissolved in water or alcohol).

$$C_7H_4O_2 \Big\langle \begin{matrix} CH(OH).N.CH_3 \\ | \\ CH_2 \rule{1em}{0.4pt} CH_2 \end{matrix} \qquad\qquad C_7H_4O_2 \Big\langle \begin{matrix} CH : N(CH_3).OH \\ | \\ CH_2.CH_2 \end{matrix}$$

<div align="center">

Hydrastinine I   *Hydrastinine II*

(carbinol form)   *(ammonium form)*

</div>
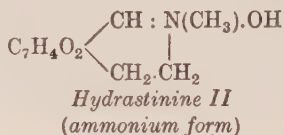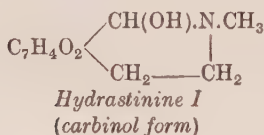
Preparation of Hydrastinine.   Hydrastinine is used in considerable quantities in medicine, and, being somewhat expensive, much attention has been given to the problem of its manufacture by methods involving more or less complete synthesis or from alkaloids such as berberine or narcotine, which are fairly plentiful and for which there is little demand.

For its preparation from hydrastine the method originally used by Freund and Will,[2] depending on hydrolytic oxidation with dilute nitric acid,[3] is available.   Using narcotine, it is necessary to prepare from this, in the first instance, cotarnine by oxidation with nitric acid, reduce the cotarnine to hydrocotarnine and then convert the latter by Pyman and Remfry's method [4] into hydrastinine.   With berberine as a starting material a process has been devised proceeding through benzyltetrahydroberberine, and the various essential steps have been covered by patents.[5]   Probably all the hydrastinine of commerce is still made from natural alkaloids, but Decker in particular has devoted much attention to processes for its preparation from simpler materials, thus he has shown that formylpiperonylamine, $CH_2 : O_2 : C_6H_3CH_2.CH_2.NH.CHO$, obtained by heating homopiperonylamine formate at $160°$–$170°$, when heated with phosphoric oxide in toluene yields 6 : 7-methylenedioxy-3 : 4-di-

    [1] *Trans. Chem. Soc.* 1904, **85,** 1006.

    [2] *Berichte,* 1887, **20,** 88.

    [3] Anderson, *Annalen,* 1853, **86, 187.**

    [4] *Trans. Chem. Soc.* 1912, **101,** 1595.

    [5] Freund, German Patents 241,136, 242,217, 242,573, 259,873 (Merck) (*Chem. Soc. Abstr.* 1912 [i], 383, 487 ; 1913 [i], 1095 ; and *Annalen,* 1913, **397,** 30.

hydro*iso*quinoline, which with methyl iodide is converted into hydrastinine hydriodide.[1]

The combination of the formulæ for hydrastinine and opianic acid (p. 280) to represent the parent alkaloid, hydrastine, may be made in several ways. Thus Freund,[2] taking into consideration the fact that the two products of hydrolysis each contained an aldehyde group whilst hydrastine itself had none, suggested that the combination must occur by condensation between these two groups, and in this way arrived at the following representation (I) :

(I)
Hyarastine (Freund)
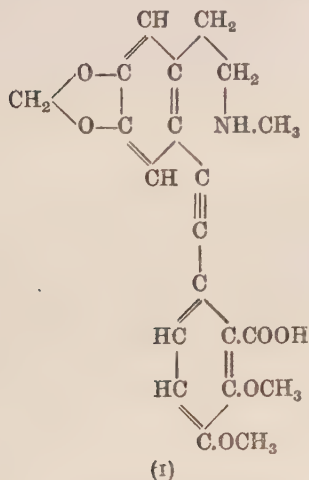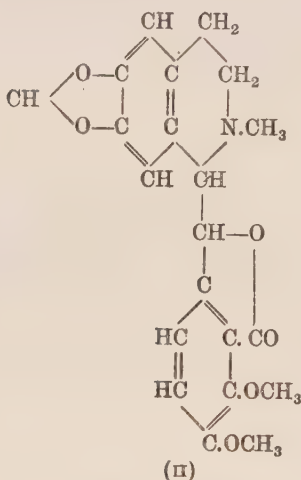
(II)
Hydrastine (Roser)

This formula represents hydrastine as both a secondary amine and a free acid, though the alkaloid reacts with alkyl iodides on the whole as a tertiary amine and forms salts with alkalis rather as a lactone than as a free acid. These and other considerations led Roser to suggest the alternative formula (II) which is in better

[1] Decker and collaborators, German Patents 234,850, 245,523, 267,699 (*Chem. Soc. Abstr.* 1911 [i], 906 ; 1914 [i], 198). For other similar syntheses of hydrastinine and its homologues or related substances *see* Decker and collaborators, *Berichte,* 1909, **42,** 2075 ; *Annalen,* 1913, **395,** 299, 321, 328, 342 ; Pictet and Kay, *Berichte,* 1909, **42,** 1973 ; Freund, *ibid.* 1911, **44,** 2356 ; Kaufmann and collaborators, *ibid.* 1913, **46,** 2929 ; 1916, **49,** 675 ; 1917, **50,** 1630 ; E. Merck, German Patents 279,194, 280,152 (*Chem. Soc. Abstr.* 1915 [i], 709, 710) ; Rosenmund, *Ber. Deut. Pharm. Ges.* 1919, **29,** 200 ; German Patents 320,840, 336,153 (*Chem. Soc. Abstr.* 1920 [i], 680 ; 1921 [i], 587) ; von Braun, *Berichte,* 1923, **56,** 690 ; *Soc. Chem. Ind. Basle ;* British Patent 191,233 (*Chem. Soc. Abstr.* 1923 [i], 371).

[2] *Berichte,* 1889, **22,** 2337.

agreement with these reactions.[1] By condensing nitromeconin with hydrastinine, Hope and Robinson [2] have prepared a *dl*-nitrohydrastine.

Berberine, $C_{20}H_{19}O_5N$. This second alkaloidal constituent of *Hydrastis canadensis* is somewhat widely distributed in the vegetable kingdom, and occurs in species belonging to a number of different natural orders. Some of the occurrences are as follows : [3]

Natural Order.		Species.
Ranunculaceae	.	*Coptis Teeta, C. trifolia, Hydrastis canadensis, H. bonadensis, Xanthorrhiza apiifolia.*
Berberidaceae	.	*Berberis vulgaris, B. Aquifolium (B. repens), B. buxifolia, B. glauca, B. aetnensis, B. nervosa,* and other species ; *Nandina domestica.*[4]
Menispermaceae	.	*Coscinium fenestratum, Archangelisia flava* and *leminiscata.*
Papaveraceae	.	*Argemone mexicana, Chelidonium majus, Stylophorum diphyllum.*
Rutaceae	.	*Xanthoxylon clava Herculis* and other species *Toddalia aculeata* and *Asiatica, Evodia meliæfolia, Phellodendron amarense.*

It has been stated to occur in *Podophyllum peltatum* rhizome, but this was disproved by Power.[5] Similarly Gordin [6] has shown that it does not occur in calumba root (p. 224), pareira brava root (p. 412), *Menispermum canadense* or *Jeffersonia diphylla.*

The alkaloid was first isolated by Chevalier and Pelletan from the bark of *Xanthoxylon clava Herculis,*[7] and called "xanthopicrit." It was found independently by Buchner and Herberger [8] in barberry root bark, *Berberis vulgaris,* and was examined by Fleitmann.[9] The formula now assigned to the alkaloid was first used by Perrins, who identified berberine with " xanthopicrit." [10]

[1] *Annalen,* 1889, **254,** 357. *Cf.* Freund and Rosenburg, *Berichte,* 1890, **23,** 404 ; Freund, *Annalen,* 1892, **271,** 311 ; and Schmidt, *Arch. Pharm.* 1893, **231,** 541 ; Rabe and McMillan, *Annalen,* 1910, **377,** 223.

[2] *Proc. Chem. Soc.* 1912, p. 17.

[3] *Cf.* Schulbach, *Inaug. Diss. Marburg,* 1886 ; Boorsma, *Bull. Inst. Bot. Buitenzorg,* 1902, **14,** 1 ; Wehmer, *Die pflanzenstoffe,* Jena, 1911.

[4] This species also contains nandinine, $C_{19}H_{19}O_4N$., described as amorphous and toxic (Eykman, *Chem. Soc. Abstr.* 1885, 565).

[5] *Amer. Journ. Pharm.* 1878, **50,** 370.

[6] *Arch. Pharm.* 1902, **240,** 146. *Cf.* Gadamer, *ibid.* p. 450.

[7] *Journ. chim. med.* 1826, **2,** 314.

[8] *Annalen, Suppl.* 1837, **24,** 228.

[9] *Annalen,* 1846, **59,** 60.

[10] *Journ. Chem. Soc.* 1862, **15,** 339.

From *Hydrastis canadensis* or other sources, berberine is usually isolated as the crude sulphate,[1] as described on p. 199. Gaze [2] recommends the acetone compound as a means of purification. To prepare this 50 grm. of crude berberine sulphate are dissolved in 1,000 grm. of water, and 500 grm. of acetone added. The mixture is then made alkaline with sodium hydroxide solution when the acetone compound is precipitated as a lemon-yellow powder.[3] For the recovery of berberine from this compound, Gaze recommended boiling 2 grm. of the substance with 50 c.c. of dry alcohol containing 5 c.c. of chloroform.

For the estimation of berberine Gordin [4] has suggested precipitation of the alkaloid as sulphate by adding alcoholic sulphuric acid to an alcoholic solution of the alkaloid ; the precipitate is subsequently suspended in water and decomposed by the addition of potassium iodide solution, by which means insoluble berberine hydriodide is precipitated and the liberated sulphuric acid is then titrated with $N/40$ potassium hydroxide solution. This method may be applied to the estimation of berberine in plants if the crude alkaloid is first purified through the acetone compound.[5] In the case of hydrastis rhizome the hydrastine must first be extracted from the rhizome by dry ether (*see* p. 201). Troeger and Linde [6] have pointed out that berberine may be estimated by precipitation with a known excess of an aqueous solution of β-naphthalenethiosulphonate, the excess of the precipitant being determined by titration of the filtrate with $N/100$ iodine solution.[7]

Berberine crystallises from water in long silky, reddish-yellow needles with $5\frac{1}{2}H_2O$; dried at $100°$, the crystals retain $2\frac{1}{2}H_2O$; from chloroform it forms triclinic tablets containing $1CHCl_3$, m.p. $179°$; the acetone compound, $B.C_3H_6O$, forms reddish-yellow tablets. It separates from ether in needles, m.p. $144°$.[8] It is soluble in cold water (1 in 4·5 at $21°$) or alcohol (1 in 100), and readily soluble in the hot liquids ; slightly soluble in benzene or chloroform, and insoluble

[1] Lloyd, *Pharm. Journ.* 1879–80 [iii], **10,** 125.

[2] *Arch. Pharm.* 1890, **228,** 604.

[3] For details of the constitution of this and similar addition products of berberine *see* Gadamer, *Arch. Pharm.* 1905, **243,** 42 ; Pyman, *Trans. Chem. Soc.* 1911, **99,** 1690 ; Robinson and Robinson, *ibid.* 1917, **111,** 958. *Cf.* Gordin and Merrell, *Arch. Pharm.* 1901, **239,** 226.

[4] *Ibid.* 1901, **239,** 638.

[5] Gordin and Prescott, *ibid.* 1899, **237,** 439.

[6] *Ibid.* 1900, **238,** 4.

[7] For other methods *see* Richter, *ibid.* 1914, **252,** 192.

[8] Gadamer, *ibid.* 1905, **243,** 33.

in ether or light petroleum. The aqueous solution is bitter to the taste, neutral to litmus, and optically inactive. The salts are formed with the loss of $1H_2O$ (*cf.* p. 215) ; they are mostly of dull yellow colour and crystallise well. The hydrochloride, $C_{20}H_{17}O_4N . HCl .$ $2H_2O$, small needles ; the hydriodide, $C_{20}H_{17}O_4N . HI$, is sparingly soluble in cold water (1 in 2130) ; the nitrate forms greenish-yellow needles and the sulphate slender yellow needles ; both these are sparingly soluble in cold water, and even less so in dilute solutions of the corresponding acids. The phosphate, $C_{20}H_{17}O_4N .$ $2H_3PO_4 . 1\frac{1}{2}H_2O$, is bright yellow and crystalline.[1] The aurichloride, platinichloride, and carbonate can be crystallised, the first from alcoholic hydrochloric acid.

An aqueous solution of berberine gives a precipitate of the characteristic crystalline nitrate on addition of nitric acid (sp. gr. 1·185). On reduction with sulphuric acid and zinc the aqueous solution becomes colourless owing to the formation of the so-called tetrahydroberberine (p. 217). Chlorine water, added to berberine hydrochloride dissolved in water, gives a reddish coloration.[2] For the detection of berberine in plants Gordin[3] recommends a method which is useful, though since it was published other alkaloids likely to give the same reactions have been described.

Constitution of Berberine. Our knowledge of the chemistry of berberine is chiefly due to W. H. Perkin, jun.[4]

When heated with hydriodic acid, berberine yields two molecular proportions of methyl iodide, and is thereby converted into BER - BEROLINE, $C_{18}H_{13}ON$. The latter is amorphous, gives an amorphous sulphate, and dissolves in alkaline solutions, forming dark violet liquids. When berberine is oxidised in warm alkaline solution with potassium permanganate, an interesting series of derivatives is obtained, of which the following are the more important : *Berberal*, $C_{20}H_{17}O_7N$; *Anhydroberberilic acid*, $C_{20}H_{17}O_8N$; *Berberilic acid*, $C_{20}H_{19}O_9N$.

Berberilic acid, $C_{20}H_{19}O_9N$, m.p. 177°–182°, crystallises from methyl alcohol on addition of water, is dibasic and furnishes a dimethyl ester, m.p. 173°. When heated to about 180°, the acid

[1] Shedden, *Pharm. Journ.* 1900 [iv], **11**, 89.

[2] For other reactions *see* Hirschhausen, *Zeit. anal. Chem.* 1885, **24**, 157.

[3] *Arch. Pharm.* 1902, **240**, 146. *Cf.* Feist, *ibid.* 1918, **256**, 1.

[4] *Trans. Chem. Soc.* 1889, **55**, 63 ; 1890, **57**, 991 ; 1910, **97**, 305.

loses $1H_2O$, and passes into ANHYDROBERBERILIC ACID, $C_{20}H_{17}O_8N$, which is one of the most easily obtained oxidation products of berberine. It forms colourless needles, m.p. 236°, soluble in alkali and alkali carbonate solutions with the formation of salts of berberilic acid. When ammonium berberilate formed in this way is dried under reduced pressure, a molecular proportion of ammonia is lost with the formation of the ammonium salt of the anhydro-acid, from which other salts have been obtained, and in particular the methyl ester, m.p. 178°. Anhydroberberilic acid appears, therefore, to be formed from berberilic acid by an intramolecular condensation between a carboxyl group and a hydrogen of a neighbouring group. When berberilic acid is heated with dilute sulphuric acid it undergoes hydrolysis thus :

$$C_{20}H_{19}O_9N \quad + \quad H_2O = C_{10}H_{10}O_6 \quad + \quad C_{10}H_{11}O_4N_8$$

Berberilic acid   *Hemipinic*   *Aminoethylpiperonyl-*
                                     acid   *carboxylic acid*
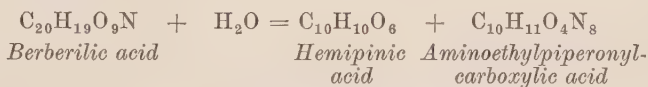
The non-nitrogenous hydrolytic product agrees in all its reactions with the hemipinic acid obtained by Goldschmiedt from narcotine and which has the constitution $C_6H_2[OCH_3 : OCH_3 : COOH : COOH = 1 : 2 : 3 : 4]$. The nitrogenous product of the hydrolysis crystallises in large tabular crystals, m.p. 180°–182°, forms well-crystallised salts with acids, and also possesses weak acid properties. When boiled with water or when heated at its melting-point it forms an anhydride, $C_{10}H_9O_3N$, which with nitrous acid gives a nitrosoamine that is decomposed by alkalis, evolving nitrogen and yielding a lactone, $C_{10}H_8O_4$, colourless needles, m.p. 126°. These changes may be represented thus :

$$C_{10}H_{11}O_4N \longrightarrow C_{10}H_8O_3 : NH \longrightarrow C_9H_6O_2 \Big\langle {{NH.NO} \atop {COOH}} \longrightarrow$$

$$C_9H_8O_2 \Big\langle {{OH} \atop {COOH}} \longrightarrow C_9H_8O_2 \Big\langle {{O} \atop {CO}}$$

Lactone, $C_{10}H_8O_4$
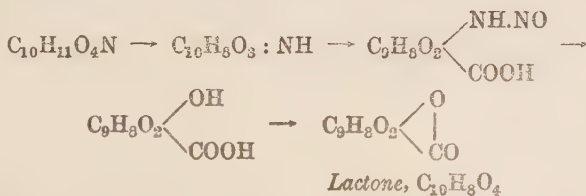
The lactone dissolves in alkalis, giving salts of the corresponding acid, $C_{10}H_{10}O_5$, and when heated in sealed tubes with dilute hydrochloric acid is decomposed with the liberation of carbon and the formation of a new crystalline substance, $C_9H_8O_4$, m.p. 220°–225°, having the characters of a substituted catechol. These reactions indicated that the lactone, $C_{10}H_8O_4$, was a piperonyl derivative I,

in which case the reaction can be regarded as taking place in the
following way :
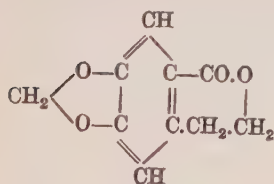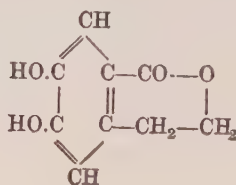
I *Lactone*, $C_{10}H_8O_4$ II   III *Oxyhydrastinine.*
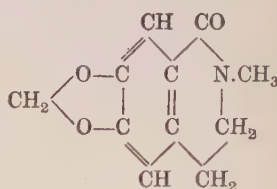
Such a substance is closely related to oxyhydrastinine (p. 203),
as comparison of formulæ I and III shows.   The proof of this
was furnished by Perkin's synthesis [1] of oxyhydrastinine from the
lactone, $C_{10}H_8O_4$, which is, therefore, ω-hydroxyethylpiperonyl-
carboxylic acid anhydride.   This synthesis was accomplished by
treating the anhydride I with phosphorus pentachloride, thereby
converting it into ω-chloroethylpiperonylcarboxylic acid chloride IV
which was then poured into absolute methyl alcohol giving the
chloromethylic ester V.   This on treatment with methylamine
formed oxyhydrastinine III.
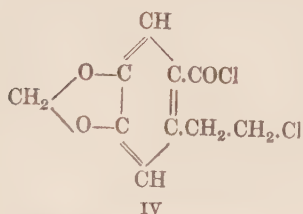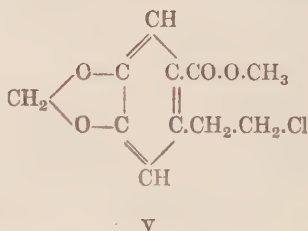
IV   V

From this synthesis it follows that the nitrogenous hydrolytic
product of berberilic acid must be ω-aminoethylpiperonylcarboxylic
acid VI.[1] By combining this formula with that of hemipinic acid
the following formula for berberilic acid is obtained :
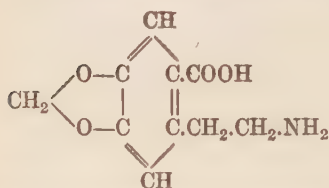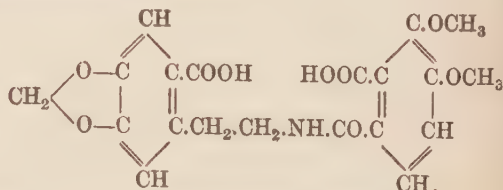
ω-*Aminoethylpiperonylcarboxylic acid* (VI)   *Berberilic acid* (Perkin)

[1] *Trans. Chem. Soc.* 1890, **57**, 1034.

The validity of this formula has been proved by the synthesis of anhydroberberilic acid from hemipinic acid and ω-aminoethyl-piperonylcarboxylic acid.

Berberal, $C_{20}H_{17}O_7N$. This substance, which is obtained from the parent alkaloid with great difficulty, crystallises in colourless glancing leaflets, m.p. 148°–150°. When hydrolysed by boiling with dilute sulphuric acid, it also furnishes ω-aminoethylpiperonyl-carboxylic acid anhydride, and a second aromatic acid, ψ-opianic acid. The latter was found to be the semi-aldehyde corresponding to hemipinic acid, and has, therefore, the constitution C_6H_2[CHO . COOH . OMe . OMe $= 1 : 2 : 5 : 6$]. It was found possible to recombine ψ-opianic acid with the anhydro-base, $C_{10}H_9O_3N$, to form berberal, and Perkin and Robinson [1] have assigned the following formula to this substance :
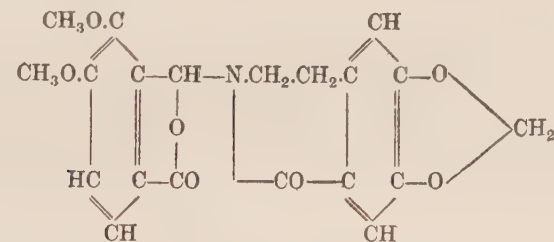
Berberal (Perkin and Robinson, 1910)

By combining opianic acid, C_6H_2[MeO : MeO : COOH : CHO $= 1 : 2 : 3 : 4$], with the same anhydride, iso*berberal*, needles, m.p. 185°, has been obtained.[1]

Oxyberberine, $C_{20}H_{17}O_5N$. This alkaloid, the first product of the action of potassium permanganate on berberine, crystallises in lustrous, colourless plates, m.p. 198°–200°, from xylene. When even traces are dissolved in 50 per cent. sulphuric acid and a drop of nitric acid is added to the solution, a deep brown colour is produced, changing to intense violet. Oxyberberine has been synthesised by Pictet and Gams (*see* p. 216).

From a consideration of these reactions Perkin assigned a formula to berberine, which has been modified by Perkin and Robinson, as shown on the top of p. 214.[1]

The necessity for at least two formulæ to represent berberine was shown by Gadamer,[2] who observed that on adding barium

[1] *Trans. Chem. Soc.* 1910, **97**, 321. *Cf.* Perkin, *ibid.* 1890, **57**, 1002.
[2] *Arch. Pharm.* 1901, **239**, 648 ; *Chem. Zeit.* 1902, **26**, 291 ; *Arch. Pharm.* 1905, **243**, 31 ; Voss and Gadamer, *ibid.* 1910, **248**, 43. *Cf.* Roser, *Chem. Zeit.* 1902, **26**, 385.

(I)

```
           C.O—CH₂
          ╱╲    |
        HC    C.O
         |     ‖
    CH  CH   C   CH
    ╱╲ ╱╲ ╱╲ ╱
  HC   C   C   C
   |   |   |   |
CH₃O.C  C   N   CH₂
   ╲╱ ╲╱‖╲╱
 CH₃O.C  CH  CH₂
         OH
```

Berberine (ammonium form)

(II)

```
           C.O.CH₂
          ╱╲    |
        HC    C.O
         |     ‖
    CH  CH   C   CH
    ╱╲ ╱╲ ╱╲ ╱
  HC   C   C   C
   |   |   ‖   |
CH₃O.C  C   NH   CH₂
   ╲╱ ╲╱ ╲╱
 CH₃O.C  CHO  CH₂
```

Berberinal (aldehyde form)
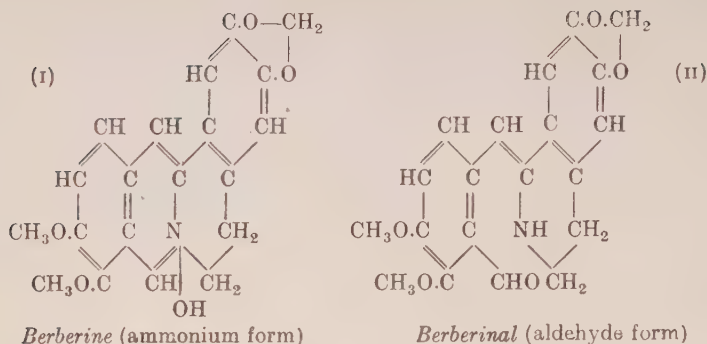
hydroxide to berberine sulphate solution, a brownish-red, strongly alkaline solution of the free base (berberinium hydroxide of Gadamer, formula I, p. 215) is obtained, which with excess of sodium hydroxide yields berberinal (supposed aldehyde form of berberine, formula II), which differs from ordinary solid berberine (ammonium form) in being soluble in ether. This furnishes an oxime, m.p. 165°, and on treatment with concentrated sodium hydroxide yields oxy-berberine, $C_{20}H_{17}O_5N$ (*see* p. 213), and the so-called dihydroberberine, $C_{20}H_{19}O_4N$, thus behaving like an aromatic aldehyde. Faltis has suggested [1] that this reaction is in reality analogous with that between quinoline methiodide and alkalis,[2] and that the products formed are oxyberberine and tetrahydroberberine (*dl*-canadine). Tinkler [3] has, however, observed that ordinary berberine and its salts show the same ultra-violet absorption spectra, whilst Gadamer's "berberinal" shows an absorption spectrum almost identical with that of Freund and Beck's α-methyldihydroberberine,[4] which would appear to be a derivative of a carbinol form of berberine. Further, the absorption spectrum of the hydro-product formed by the action of alkalis on "berberinal" is similar to that of the supposed "berberinal," and is quite distinct from that of tetra-hydroberberine, so that these observations lend no support to Faltis's suggestion. The position, therefore, is that berberine can theoretically exist in three forms, of which two are known, viz., (*a*) the *ammonium form* (I), in which berberine exists in solution when the calculated quantity of barium hydroxide is added to an aqueous solution of the sulphate or when berberineacetone is

[1] *Monats.* 1910, **31,** 557.
[2] Decker, *Berichte,* 1903, **36,** 2568.
[3] *Trans. Chem. Soc.* 1911, **99,** 1340.
[4] *Berichte,* 1904, **37,** 4677.

decomposed by superheated steam, and it is by replacement of the —OH group in this form by acid radicles that berberine salts (really quaternary compounds) are formed ; and (*b*) the *carbinol form* (III) which represents the ordinary alkaloid first isolated by Gadamer in a pure state, and for which Perkin [1] proposes to reserve the name " berberine," and which is, therefore, in this sense synonymous with Gadamer's " berberinal " and Tinkler's " berberinol." The aldehyde, form II, has not been obtained.   Dihydro- and tetrahydro-berberines on this system of nomenclature then become dihydro- and tetrahydro-anhydroberberines.[1]   The   condensed formulæ for these three forms are as follows :

$$(MeO)_2C_6H_2 \begin{cases} CH : C \text{———} C_6H_2 : O_2 : CH_2 \\ \quad | \qquad\qquad | \\ CH : N(OH).CH_2.CH_2 \end{cases}$$

Ammonium form = Perkin's Berberinium hydroxide

(I)

$$MeO)_2C_6H_2 \begin{cases} CH = C \text{———} C_6H_2 : O_2 : CH_2 \\ \quad | \qquad | \\ CHO \ NH.CH_2.CH_2 \end{cases}$$

Aldehyde form ; not known

(II)

$$(MeO)_2C_6H_2 \begin{cases} CH = C \text{———} C_6H_2 : O_2 : CH_2 \\ \quad | \qquad | \\ CHOH.N.CH_2.CH_2 \end{cases}$$

Carbinol form = Berberine

(III)
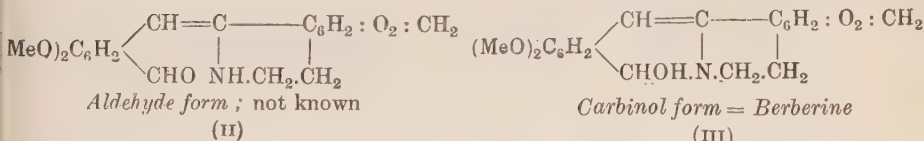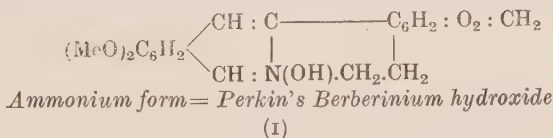
By the action of strong alkalis the carbinol form is converted into dihydroberberine (dihydroanhydroberberine, Perkin) and oxyberberine, thus :

$$(MeO)_2C_6H_2 \begin{cases} CH : C \text{—} \text{—} C_6H_2 : O_2 : CH_2 \\ \quad | \qquad | \\ CH_2.N.CH_2.CH_2 \end{cases}$$

Dihydroberberine

$$(MeO)_2C_6H_2 \begin{cases} CH : C \text{———} C_6H_2 : O_2 : CH_2 \\ \quad | \qquad | \\ CO . N.CH_2.CH_2 \end{cases}$$
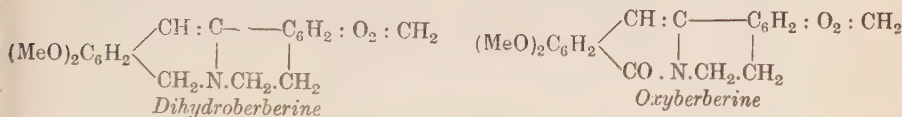
Oxyberberine

Bland, Perkin and Robinson have shown that on treating oxyberberine with hydrochloric acid, it is converted into *isooxy-berberine*, apparently by the opening of the reduced pyridine ring,[2] thus :

$$\begin{cases} : C \text{———} C_6H_2 \text{—} \\ \quad | \qquad | \\ .CO.N.CH_2.CH_2 \end{cases} \quad \rightarrow \quad \begin{cases} : C \text{———} C_6H_2 \text{—} \\ \quad | \qquad | \\ .CO.NH \quad CH : CH_2 \end{cases}$$

A third isomeride, neo-oxyberberine, was obtained by Pyman [3]

[1] *Trans. Chem. Soc.* 1918, **113**, 503.
[2] *Ibid.* 1912, **101**, 262.
[3] *Ibid.* 1911, **99**, 1692.

by the oxidation of berberineacetone with permanganate in acetone solution. Its formation may be shown by partial formulæ as follows, which represent it as a phenolbetaine, and in harmony with that view it forms with methyl iodide methoxyberberinium iodide :

.CH══════════C.
|
.CH(CH₂.CO.CH₃).N.CH₂.CH₂.
Berberineacetone

→

.CO──────────CH──
|
.CH(CH₂.CO.CH₃).N.CH₂.CH₂.
Neo-oxyberberineacetone

→

.C════C──
\
O |
\
.CH══N.CH₂.CH₂── .
Neo-oxyberberine

→

.C(OCH₃)═C──
|
.CH══════N(I).CH₂.CH₂
Methoxyberberinium iodide
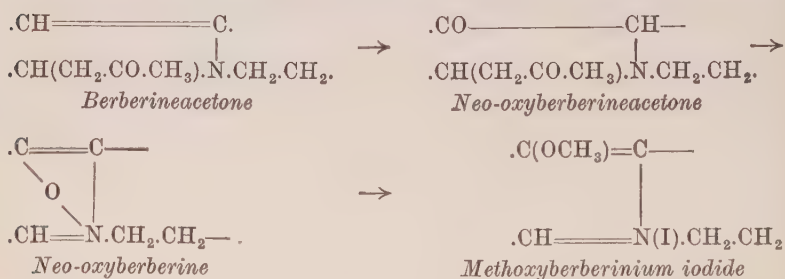
Synthesis of Oxyberberine.[1] Bouveault and Wahl showed that piperonal condenses with nitromethane in presence of sodium methoxide and methyl alcohol to yield piperonylidenenitromethane ; this, on oxidation, furnishes homopiperonaldoxime,[2] which Medin-

(I)

(II)

(III)
Oxyberberine
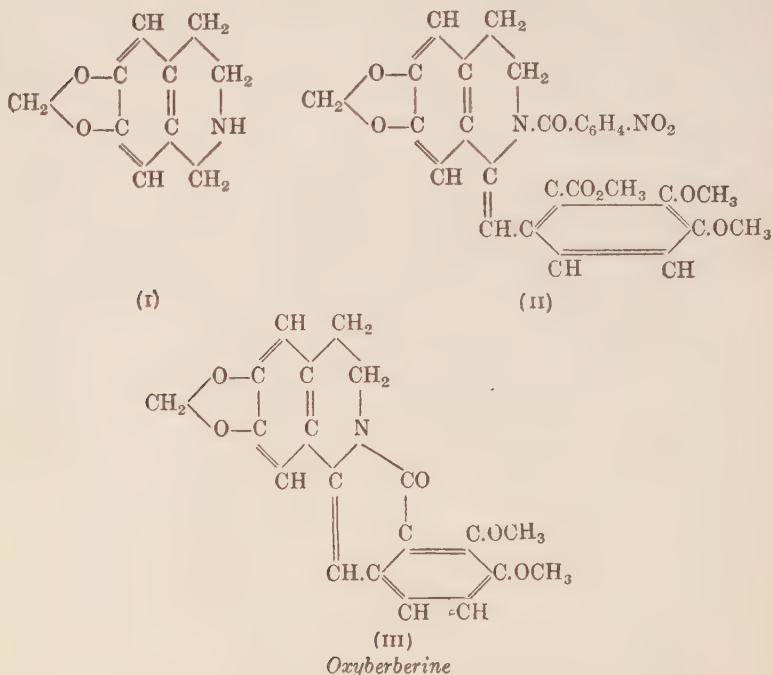
[1] Pictet and Gams, *Compt. rend.* 1911, **152**, 1102 ; **153**, 386.
[2] *Compt. rend.* 1902, **135**, 41.

ger [1] found was reduced by sodium and alcohol to homopiperonyl-amine : $CH_2 : O_2 : C_6H_3.CH_2.CH_2.NH_2$.

Pictet and Gams treated this amine with formaldehyde in presence of hydrochloric acid, thereby converting it into methylene-dioxytetrahydro*iso*quinoline (norhydrohydrastinine) (I). The *o*-nitro-benzoyl derivative of this reacts with the methyl ester of opianic acid in presence of sulphuric acid, to give the compound (II) which crystallises in needles, m.p. 103°–105°, and on treatment with potassium hydroxide in alcohol yields Perkin's oxyberberine (III) by hydrolysis and subsequent elimination of water between the carboxyl- and imino-groups. Perkin [2] subsequently showed that oxyberberine can be reduced electrolytically to tetrahydro-(anhydro)-berberine, and, as the latter can be converted into berberine, this forms a complete synthesis of the latter alkaloid.

Synthesis of Berberine. This was accomplished by Pictet and Gams [3] by an extension of the method just described. Homo-veratroylhomopiperonylamine, $CH_2 : O_2 : C_6H_3.CH_2.CH_2.NHCO.$ $CH_2.C_6H_3(OCH_3)_2$, loses $1H_2O$ when heated with phosphoric anhydride in xylene, forming the compound (I) which on reduction with tin and hydrochloric acid furnishes veratroylnorhydro-hydrastinine (II). On treating this with methylal in presence of hydrochloric acid, a —CH_2 group is inserted between the veratroyl ring and the imino group, yielding tetrahydroberberine (III), and this on oxidation yields berberine (IV). These steps are shown by the following condensed formulæ :

$$(MeO)_2.C_6H_3 \diagup \begin{matrix} CH_2.C\text{——}C_6H_2 : O_2 : CH_2 \\ \| \quad | \\ N.CH_2.CH_2 \end{matrix} \rightarrow (MeO)_2.C_6H_3 \diagup \begin{matrix} CH_2.CH\text{——}C_6H_2 : O_2 : CH_2 \\ | \quad | \\ NH.CH_2.CH_2 \end{matrix} \rightarrow$$
$$\text{(I)} \qquad\qquad\qquad\qquad \text{(II)}$$

$$(MeO)_2.C_6H_2 \diagup\!\!\!\diagdown \begin{matrix} CH_2.CH\text{——}C_6H_2 : O_2 : CH_2 \\ | \quad | \\ CH_2.N.CH_2.CH_2 \end{matrix} \rightarrow (MeO)_2.C_6H_2 \diagup\!\!\!\diagdown \begin{matrix} CH\!\!=\!\!C\text{——}C_6H_2 . O_2 : CH_2 \\ | \quad | \\ CHOH.N.CH_2.CH_2 \end{matrix}$$
$$\text{(III)} \qquad\qquad\qquad\qquad\qquad \text{(IV)}$$

T etrahydroberberine (Canadine)   *Berberine*
T etrahydroanhydroberberine (Perkin)
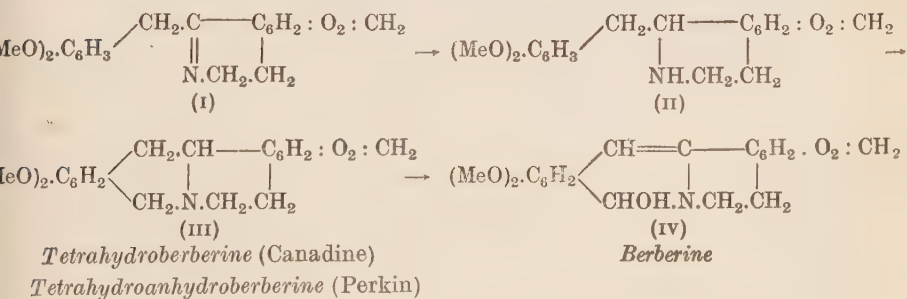
By the application of the Grignard reaction to berberine

[1] *Monats.* 1906, **27**, 237.
[2] *Trans. Chem. Soc.* 1918, **113**, 737.
[3] *Loc. cit.*

Freund and collaborators have prepared a series of α-alkyldihydro-berberines.[1]

Canadine, $C_{20}H_{21}O_4N$. In 1873 Hale[2] obtained indications of a third alkaloid in *Hydrastis canadensis*, which was isolated in a pure state and named " canadine " by Schmidt and Wilhelm.[3] It is best separated from crude hydrastine by fractional crystallisation of the nitrates, canadine nitrate being less soluble than the hydrastine salt.[4] The alkaloid forms silky needles, m.p. 133°–134°, $[\alpha]_D$ — 299° in chloroform, insoluble in water, but readily soluble in ether. The hydrochloride, B.HCl, and nitrate, B.HNO₃, are crystalline, lævorotatory, and slightly soluble in water. Canadine gives an olive-green colour changing to brownish-black with sulphovanadic acid, and a similar colour changing to brownish-red with Fröhde's reagent.

Gadamer,[5] by fractional crystallisation of tetrahydroberberine bromocamphorsulphonate, has isolated a lævorotatory alkaloid identical with canadine, which is, therefore, to be regarded as *lævo*-tetrahydroanhydroberberine (*see* III, p. 217).

The isomerism of the ammonium bases derived from tetrahydro-anhydroberberine was first investigated by E. Schmidt and pupils,[6a] and later by Voss and Gadamer,[7] who pointed out that three types of anhydro-base may be expected when an alkoxide of this alkaloid is heated, depending on the fact that the —OH group originally attached to the N atom may migrate to any one of the three neighbouring carbon atoms (marked 1, 2 and 3 in formula B), giving rise to carbinol bases, two of which (carbinol bases with the OH group attached to carbons 1 and 2 in formulæ A and C) may lose the elements of a molecule of water giving rise to anhydro-bases (formulæ E and F), which, however, are not true anhydro-bases of tetrahydroanhydroberberine, as Schmidt[6b] had already found, while the C(3)-carbinol base (formula D) would not readily lose water.

[1] *Berichte*, 1904, **37**, 3334, 4673 ; 1907, **40**, 2604. *Cf.* E. Merck, German Patents, 179212 and 259,873 (*Chem. Soc. Abstr.* 1913 [i]. 1095). *Annalen*, 1913, **397**, 1, 30, 52, 57, 70, 85, 94, 107 ; 1915, **409**, 188 ; 1916, **411**, 1.

[2] *Amer. Journ. Pharm.* 1873, **45**, 247. *Cf.* Lerchen, *Jahresberichte*, 1878, 144 ; and Burt, *Pharm. Journ.* 1875–76 [iii], **6**, 467.

[3] *Arch. Pharm.* 1888, **226**, 329.

[4] Schmidt, *ibid.* 1894, **232**, 136.

[5] *Ibid.* 1901, **239**, 648 ; Voss and Gadamer, *ibid.* 1910, **248**, 43.

[6] *Arch. Pharm.* (*a*) 1890, **228**, 596, 604 ; (*b*) 1892, **230**, 287, 291.

[7] *Ibid.* 1910, **248**, 43.

CH$_2$
(1)
CHOH—C══C
NR——CH$_2$—CH$_2$
(2)
CH$_2$
(3)
(1)
(A) C-*carbinol base*

←

CH$_2$
(1)
C   CH—C══C
‖
C   NR—CH$_2$—CH$_2$
(2)
CH$_2$ HO
(3)
(B) *Tetrahydroanhydro-*
berberine alkoxide

→

CH$_2$
C   CH—C══C
‖
C   NR   CH$_2$OH—CH$_2$
CH$_2$
(2)
(C) C-*carbinol base*

↓

CH
CH—C══C
NR—CH$_2$—CH$_2$
CH$_2$
(1)
(E) C-*anhydro base*

↓

CH$_2$
C   CH—C══C
‖
C   NR—CH$_2$—CH$_2$
CH$_2$OH
(3)
(D) C-*carbinol base*

↓

CH$_2$
C   CH—C══C
‖
C   NR   CH$_2$══CH
CH$_2$
(2)
(F) C-*anhydro base*
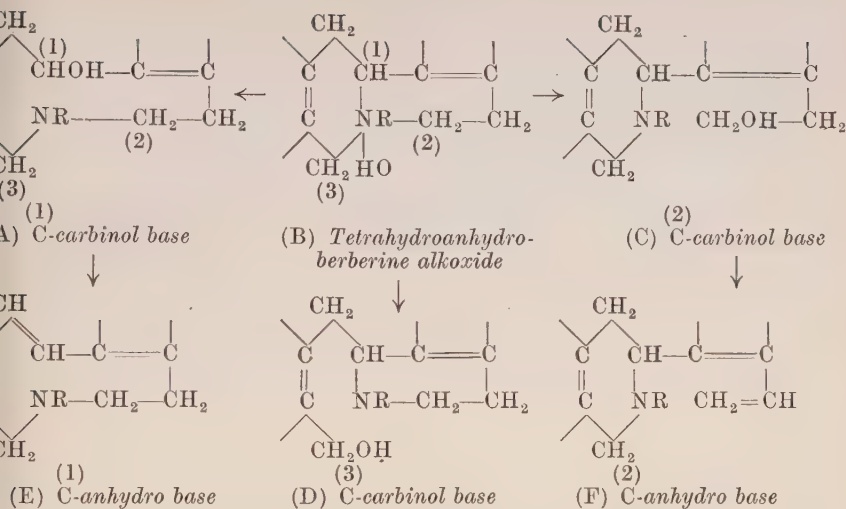
Voss and Gadamer [1] found that when the ethylcarbonate of either *dl*-tetrahydroanhydroberberine or its *l*-component (*l*-canadine ethohydroxide) was dried to constant weight *in vacuo* the same optically inactive anhydro-base was formed, and concluded that the latter must be represented by formula E (R = Et). McDavid, Perkin and Robinson,[2] thought this unlikely, and in giving an account of the exhaustive alkylation of berberine, using in the first stage benzyl chloride, and in the second and third stages methyl iodide (obtaining eventually benzyldimethylamine and the non-nitrogenous compound berberilene) described N-benzyl*iso*tetra-hydroanhydroberberine, which they represented by formula F (R = C$_7$H$_7$).

The subject was then fully investigated by Pyman,[3] who found that the products obtained depended partly on the material started with and partly on the conditions of the experiment. Thus under his conditions *l*-canadine methohydroxide when dried *in vacuo* gave rise to three anhydro-bases A and B optically inactive, and C optically active, whilst the methohydroxide of the *dl*-base formed only two, A and B, but the proportion of B formed in this instance was equal to the amount of B and C together in the case of the *l*-base (canadine). For this and other reasons, B was regarded as the racemic

[1] *Arch. Pharm.* 1910, **248**, 43.
[2] *Trans. Chem. Soc.* 1912, **101**, 1220.
[3] *Ibid.* 1913, **103**, 817. *Cf.* Freund and Fleischer, *Annalen*, 1915, **409**, 188.

form of C, and, like it, is represented by formula F above, whilst formula E is assigned to base A. The whole course of the reaction is explained by Pyman by the following scheme, in which it will be seen that base A is liable to conversion into base B, which takes place when the drying is conducted at atmospheric pressure, so that under these conditions the *dl*-base gives only anhydro-base B, and the *l*-base a mixture of anhydro-bases B and C, A disappearing entirely.

l-Canadine metho-hydroxide.   Base *A*.   *dl*-Tetrahydroberberine methohydroxide.

Base *C*.   Base *B*.
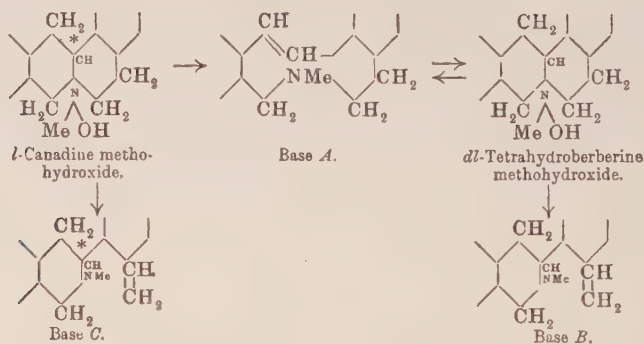
• An asterisk over the asymmetric carbon atom denotes that the compounds are optically active.

ALKALOIDS OF BERBERIS SPECIES

The root barks of *Berberis vulgaris* and of *B. aquifolium* are used in medicine, the former in Europe, and the latter in the United States. *B. vulgaris* contains three alkaloids, berbamine, berberine, and oxyacanthine.[1] Parsons,[2] Stübbe and Rüdel,[3] have shown that the same three alkaloids occur in *B. aquifolium*.[4] The berberine is best isolated as the sulphate as described already. Berbamine and oxyacanthine remain in the mother liquors, and are removed by addition of sodium hydroxide solution, and extraction by ether, the residue left on evaporation of the solvent being dissolved in acetic acid. From this solution, oxyacanthine sulphate is precipitated by sodium sulphate, and from the filtrate berbamine nitrate is precipitated with sodium nitrate. The alkaloids are regenerated, converted into the hydrochlorides, and these recrystallised from water.

[1] Polex, *Arch. Pharm.* 1836 [ii], **6**, 271 ; Wacker, *Jahresb.* 1861, 545 ; Hesse, *Berichte*, 1886, **19**, 3190.

[2] *Pharm. Journ.* 1882–83 [iii], **13**, 46.

[3] *Arch. Pharm.* 1891, **229**, 631.

[4] *Cf.* Pommerehne, *ibid.* 1895, **233**, 127.

Berbamine, $C_{18}H_{19}O_3N$. This alkaloid crystallises with $2H_2O$ from alcohol in small leaflets, m.p. 156° (*dry*), or anhydrous from light petroleum in warty masses, m.p. 197°–210°. The salts crystallise well. The sulphate, $B_2.H_2SO_4,4H_2O$, forms small leaflets or needles, the platinichloride, $B_2.H_2PtCl_6.5H_2O$, is a crystalline yellow precipitate ; the aurichloride is amorphous.

According to Rüdel [1] berbamine gives the same colour reactions as oxyacanthine, and is probably the next lower homologue of that alkaloid.

Oxyacanthine, $C_{19}H_{21}O_3N$. This substance crystallises from alcohol in needles, m.p. 208°–214° (Hesse), 202°–204° (Rüdel), or from light petroleum in warty masses, m.p. 175°–185° (Rüdel), $[\alpha]_D + 174°$ 5′ in alcohol, $+ 131·6°$ in chloroform. The hydrochloride, $B,HCl,2H_2O$, forms colourless needles, $[\alpha]_D + 163·6°$ in water ; the nitrate, $B.HNO_3,2H_2O$, small needles, m.p. 195°–200° (*decomp.*), is sparingly soluble in water. The platinichloride and aurichloride are amorphous.

According to Hesse, oxyacanthine is converted by alcoholic potassium hydroxide into the potassium salt of β-oxyacanthine, from which oxyacanthine is reformed by adding a large excess of acid. Pommerehne [2] has shown that one oxygen atom is present as a hydroxyl group, and the other two as methoxyl groups, and that the base forms a methiodide, m.p. 248°–250° (*dry*).

Oxyacanthine dissolves in nitric acid, forming a yellowish-brown solution, is not coloured by sulphuric acid, but on further addition of nitric acid a yellow coloration changing to red is observed. Molybdic acid in sulphuric acid gives a dirty violet tint, changing to yellowish green. Bromine water gives a yellow precipitate. Oxyacanthine liberates iodine from potassium iodide in dilute acid solution and gives a blue coloration with a mixture of potassium ferricyanide and ferric chloride.

Physiological Action. HYDRASTINE first stimulates the centres of the medulla oblongata, producing slowing of the pulse, constriction of blood-vessels, increased blood-pressure, and quickened respiration. Large doses eventually paralyse the medulla and the spinal cord. Apart from this action on the central nervous system, it weakens and paralyses the heart in mammals. In spite of its similarity to narcotine in constitution, hydrastine exercises no narcotic effect. It appears to be excreted in the urine unchanged.

[1] *Arch. Pharm.* 1891, **229**, 631.
[2] *Cf.* Pommerehne, *ibid.* 1895, **233**, 127.

Hydrastine has been used as an internal styptic, as in uterine hæmorrhage, but for such purposes hydrastinine (*see below*) is preferable, since it causes greater constriction of the peripheral blood-vessels and has less action on the heart.

Hydrastis rhizome has been used as a stomachic, probably owing to the berberine it contains, but is also employed, like hydrastine, as an internal styptic.

In its physiological action HYDRASTININE differs from hydrastine in causing no disturbance of the centres of motion and feeling, except in very large doses, which paralyse the nervous system. The arterial tension is increased even more than by hydrastine, and the effect lasts longer because there is no depression of the heart. It appears to have no direct action on uterine muscle, and its efficacy in arresting uterine hæmorrhage appears to be due to constriction of the blood-vessels. When applied to the eye in 10 per cent. solution it causes dilatation of the pupil. The alkaloid is used in medicine as an internal styptic.

Berberine is not toxic in the ordinary sense to the larger animals and man. In rabbits it produces respiratory disturbance and paresis. Drugs containing berberine, *e.g.*—barberry bark—have been used chiefly as tonics and stomachics.

Canadine in small doses causes drowsiness and depression. In large quantities it gives rise to transient excitement succeeded by depression and paralysis of the central nervous system. Its injection is followed by violent peristalsis of the intestine with diarrhœa. It is said to have no influence on the blood-pressure.

ALKALOIDS OF ZANTHOXYLUM SPECIES

Of the species of Zanthoxylum, which have been chemically examined, all have been found to contain alkaloids, but, with the exception of the four dealt with below, only in traces.[1]

Z. Clava-Herculis, Linn, according to Perrins,[2] contains berberine.

Z. ochroxylon D.C. Leprince [3] states that the bark of this South American plant contains two alkaloids allied to berberine. The first, α-XANTHERINE, $C_{24}H_{23}O_6N$, crystallises from benzene in colourless needles, m.p. 186°–187°, becomes yellow on exposure to

[1] For a discussion of the phyto-chemistry of this genus *see* Goodson, *Bio.-Chem. Journ.* 1921, **15**, 123, and Bocquillon, *Rep. Pharm.* 1917, **28**, 66 (*Chem. Soc. Abstr.* 1917 [i] 276) ; also Dieterle, *Arch. Pharm.* 1919, **257**, 260.

[2] *Journ. Chem. Soc.* 1862, **15, 339.**

[3] *Bull. Sci. Pharm.* 1912, **18**, 337.

air and gives yellow salts. It is stated to paralyse the intracardial nervous system. The second, β-XANTHERINE, for which no formula is given, differs from the α-alkaloid mainly in the greater solubility of its hydrochloride in water.

Z. senegalense D.C. The bark of this tree was examined by Giacosa and Soave,[1] who isolated from it two alkaloids, the first, ARTARINE, $C_{21}H_{23}O_4N$ or $C_{20}H_{17}O_4N$, amorphous, but yielding yellow crystalline salts; hydrochloride, $B.HCl.4H_2O$, needles, m.p. 194°, platinichloride, $(B.HCl)_2.PtCl_4$, bright yellow needles, m.p. above 290°, and the second present only in traces, and to which no name or formula is assigned, forms blood-red needles and yields yellow salts.

Zanthoxylum brachyacanthum, F. Muell

The bark of this species, which occurs in Queensland, was examined by Jowett and Pyman,[2] who isolated from it 1·85 per cent. of *l*-canadine-α-methochloride and 0·06 per cent. of γ-homochelido-nine. The bark was exhausted with a dilute solution of tartaric acid, the extract concentrated, the alkaloids precipitated with mercuric chloride, the washed precipitate suspended in water and decomposed by hydrogen sulphide and the filtrate from this concentrated to low bulk, made alkaline with sodium hydroxide solution and the alkaloids removed by chloroform. The dry chloroform extract was treated with dilute hydrochloric acid, the filtered acid solution made alkaline with sodium carbonate and completely extracted with ether, which removed γ-homochelidonine. The aqueous mother liquor was then mixed with sodium hydroxide solution and extracted with chloroform, which removed *l*-canadine-α-methochloride. The latter was obtained in a crystalline condition by mixing the dry chloroform extract with acetone and purified by crystallising from strong and finally dry alcohol.

l-**Canadine-α-methochloride,** $C_{21}H_{24}O_4NCl.H_2O$, crystallises in colourless prismatic needles, m.p. 262° (*corr.*), $[\alpha]_D — 1370.°$ (in water, $c = 4·197$), is readily soluble in water or hot alcohol, but insoluble in acetone. On adding potassium iodide to its solution in water *l*-canadine-α-methiodide, $C_{21}H_{24}O_4NI$, is obtained and can be crystallised from hot water, from which it separates in prisms. It melts at 220°, but when kept at this temperature crystallises and then remelts at 250° (*decomp.*). Mention has already been made

[1] *Gazz. chim. Ital.* 1887, **17**, 362; 1889, **19**, 303.
[2] *Trans. Chem. Soc.* 1913, **103**, 291, 825.

of the fact that tetrahydroanhydroberberine contains an asymmetric carbon atom and a N-atom attached to three different groups, and that Gadamer [1] had resolved it into two optically active forms, the *l*-form being identical with *l*-canadine from Hydrastis root (p. 218). From this Voss and Gadamer [2] prepared by addition of ethyl iodide two ethiodides [3] (α and β, m.p. 187° and 225°, $[\alpha]_D - 91.5°$ and $- 115.3°$ respectively), and two ethochlorides ($\alpha =$ m.p. 233°, $[\alpha]_D - 127.3°$; $\beta =$ m.p. 245°, $[\alpha]_D - 138.3°$). Jowett and Pyman prepared the α- and β-*l*-canadine methochlorides [$\alpha =$ m.p. 262°, $[\alpha]_D - 136.4°$; β, m.p. 262°, $[\alpha]_D - 160.9°$] and methiodides [$\alpha =$ m.p. 220°, $\beta =$ m.p. 264°], and satisfied themselves that the *l*-canadine-α-methochloride was identical with the alkaloid from *Z. brachyacanthum*. This is the first occasion on which a substance containing an asymmetric nitrogen atom has been isolated from a plant. The physiological action of the α- and β-methiodides was examined by Laidlaw, who found that both had the curare-like action common to ammonium bases, the β-methochloride being much more active than the α-methochloride; the relative activities of the four optically active isomerides is given as $l\alpha : d\alpha : l\beta : d\beta = 1 : 9 : 12 : 28$.

ALKALOIDS OF CALUMBA ROOT

Calumba root, derived from *Jateorhiza columba* (*Jatrorrhiza columba*), has been examined by Gunzel [4] and by Feist, [5] and shown to contain three quaternary bases, none of which has been obtained in a free state.

Columbamine. The iodide $C_{21}H_{22}O_5NI$ is yellow, and has m.p. 224°; the chloride crystallises with $2.5H_2O$ in yellow needles, m.p. 191°, and with $4H_2O$ in brown prisms, m.p. 184°; the nitrate $B.NO_3.2\frac{1}{2}H_2O$, forms lemon yellow needles, m.p. 232°, and the aurichloride slender needles, m.p. 220° (*decomp.*). Concentrated solutions of the nitrate or sulphate on decomposition by strong aqueous caustic potash solution liberate anhydrocolumbamine which crystallises in violet-black prisms, m.p. 190° (*approx., decomp.*). Columbamine nitrate or iodide on reduction yields tetrahydro-columbamine which is colourless and gives colourless crystalline salts.

[1] *Arch. Pharm.* 1901, **239**, 648.
[2] *Ibid.* 1910, **248**, 43.
[3] For nomenclature, *see* Scholz, *Berichte*, 1905, **38**, 595.
[4] *Arch. Pharm.* 1906, **244**, 257.
[5] *Ibid.* 1907, **245**, 586; and with Sandstede, 1918, **256**, 1.

Columbamine contains one hydroxyl group, four methoxyl groups, and its methyl ether on oxidation with alkaline permanganate yields corydaldine (p. 235), and an acid assumed to be $3 : 4 : 5$-trimethoxy-*o*-phthalic acid.

Jatrorrhizine.[1] The iodide, $C_{20}H_{20}O_5NI.H_2O$, crystallises in reddish-yellow needles, m.p. $208°–210°$; the chloride with $1H_2O$ from alcohol in copper coloured needles, m.p. $206°$; the nitrate in glistening golden-yellow needles, m.p. $225°$ (*decomp.*). This last-named salt yields on reduction tetrahydrojatrorrhizine, colourless needles, m.p. $206°$. Jatrorrhizine contains two hydroxyl and three methoxyl groups, and on methylation yields columbamine methyl ether, so that columbamine is a methyl ether of jatrorrhizine.

Palmatine. The iodide, $C_{21}H_{22}O_4NI.2H_2O$, m.p. $240°$, crystallises in slender yellow needles, and the nitrate, m.p. $239°$, in greenish-yellow needles. Both these salts on reduction yield tetrahydro-palmatine, $C_{21}H_{25}O_4N$, colourless leaflets, m.p. $144°$, the $d-$ form of which occurs in corydalis roots (p. 238). Palmatine contains four methoxyl groups, and, like berberine, forms addition compounds with acetone and chloroform. On oxidation by alkaline permanganate it yields corydaldine (p. 235), and *o*-hemipinic acid ($3 : 4$-dimethoxy-*o*-phthalic acid).

Constitution of the Calumba Alkaloids

The salient facts bearing on the constitution of these three alkaloids are : (1) they are all coloured quaternary bases closely resembling berberine, and on reduction yield colourless tetrahydro-bases very like corydaline in general behaviour and tertiary in character ; (2) they all yield corydaldine (I) on oxidation, the other product being hemipinic acid (II) in the case of palmatine and an acid, probably $3 : 4 : 5$-trimethoxy-*o*-phthalic acid (III), in the case of columbamine methyl ether (jatrorrhizine dimethyl ether).

It is clear that if these formulæ are correct, it should be possible to convert berberine into palmatine by replacing the dioxy-methylene group of the former by two methoxyl groups, and though Feist and Sandstede [2] failed to effect this, Späth and Lang [3] succeeded to a limited extent in converting tetrahydroberberine into tetrahydropalmatine by heating the former with potassium hydroxide in methyl alcohol and methylating the resulting product

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[1] Originally named " jateorhizine " by Feist.
[2] *Arch. Pharm.* 1918, **256,** 1.
[3] *Berichte,* 1921, **54,** 3064.

CH
CH C.OCH$_3$
C C.OCH$_3$
CH C
CH C CH
CH$_3$O.C C N.OH
CH$_3$O.C C CH$_2$
CH CH$_2$

Palmatine base

$\longrightarrow$

C.OCH$_3$
COOH.C C.OCH$_3$
COOH.C CH
CH

(II) *Hemipinic acid*

C.OCH$_3$
CH C.OCH$_3$
C C.OCH$_3$
CH C
CH C CH
CH$_3$O.C C N.OH
CH$_3$O.C C CH$_2$
CH CH$_2$

Columbamine methyl ether base

CH C:O
CH$_3$O.C C NH
CH$_3$O.C C CH$_2$
CH CH$_2$

(I) *Corydaldine*

CH
CH$_3$O.C C.COOH
CH$_3$O.C C.COOH
C.OCH$_3$

(III) 3 : 4 : 5-*trimeth-oxyphthalic acid*
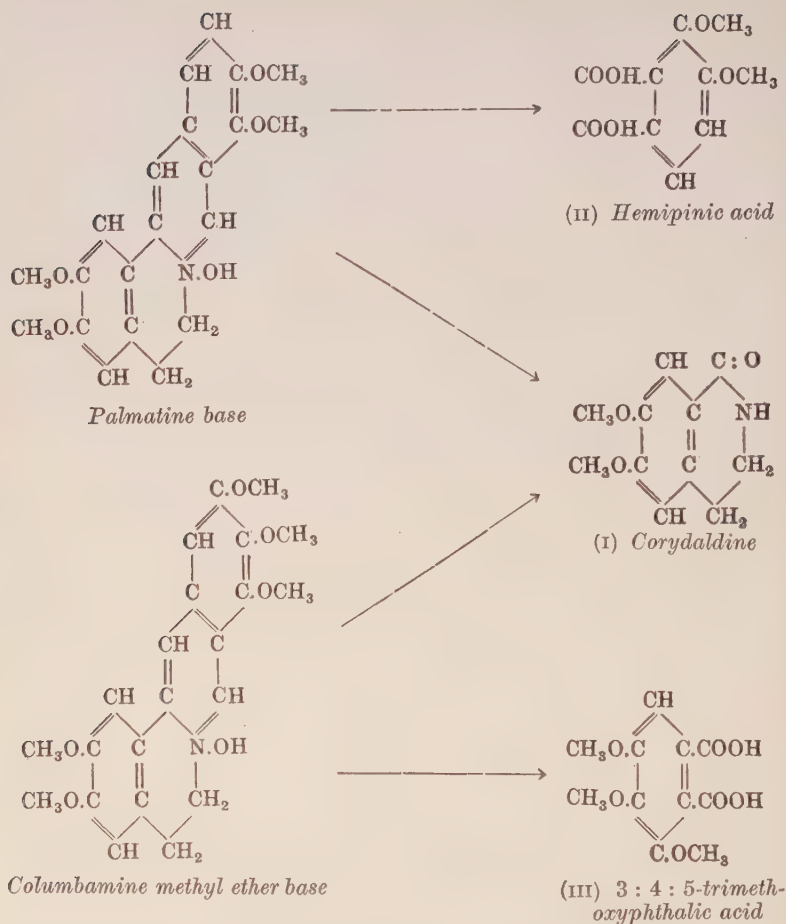
with methyl sulphate and alkali in absence of oxygen, when on addition of potassium iodide, tetrahydropalmatine methiodide resulted, which on heating *in vacuo* yielded tetrahydropalmatine, and this on oxidation with iodine gave palmatine. The same authors [1] by the use of magnesium methyl iodide converted palmatine iodide into α-methyldihydropalmatine, yellow needles, m.p. 128°–130°, and this on reduction yielded two α-methyltetrahydropalmatines m.p. 165°, and m.p. 67°–69°, neither of which was identical with meso- or *r*-corydaline indicating that the —CH$_3$ group in corydaline is not in the position assigned to it by Dobbie and Lauder (p. 237).

[1] *Berichte*, 1921, **54**, 3074.

Späth and Böhm [1] have also attempted the synthesis of tetra-hydrocolumbamine methyl ether (tetrahydrojatrorrhizine dimethyl ether), and though they obtained a substance which has the constitution assigned to this base by Feist, it was not identical with it. They then re-examined columbamine and jatrorrhizine and their fully methylated product, and came to the conclusion that the latter was identical with palmatine and its tetrahydro-derivative with tetrahydropalmatine. They are doubtful, therefore, of the homogeneity of columbamine and jatrorrhizine and suggest that calumba roots contain palmatine and other bases in which one or more of the methoxyl groups of palmatine are replaced by hydroxyl groups or by phenolic oxygen united to a readily eliminable complex.

Physiological Action. According to Biberfeld [2] palmatine, columbamine and jatrorrhizine all paralyse the central nervous system in frogs ; palmatine also produces this result in mammals, and is distinguished from the other two in stopping respiration, probably by paralysis of the respiratory centre. All three alkaloids lower the blood-pressure on intravenous injection, and this is especially marked in the case of palmatine.

ALKALOIDS OF *LYCORIS RADIATA*

Lycorine, [3] $C_{16}H_{17}O_4N$, was obtained from the bulbs of this Japanese plant by Morishima, [4] who assigned to it the formula, $C_{32}H_{32}O_8N$. Ewins subsequently isolated from the bulbs of *Narcissus pseudonarcissus* (wild daffodil) and *N. princeps*, an alkaloid of the formula, $C_{16}H_{17}O_4N$, which he named " narcissine," [5] and under this name it was again isolated from *Buphane disticha* by Tutin [6] (p. 229). In 1913, Asahina and Sugii [7] pointed out that these two alkaloids were probably identical, and this was confirmed by Gorter [8] in 1919, who further showed that the same alkaloid occurred in the following plants belonging to the same order (Amaryllidaceae) :

[1] *Berichte*, 1922, **55**, 2985.

[2] *Zeits. Exp. Path. Pharm.* 1910, **7**, quoted in *Arch. Pharm.* 1918, **256**, 31.

[3] Gorter adopted the name " lycorine," but " narcissine " strictly has priority, since Gerrard, in 1878, called his base " narcissia," and Ewins quite correctly used this in the modern form, " narcissine."

[4] *Arch. exp. Path. Pharm.* 1897, **40**, 121.

[5] *Trans. Chem. Soc.* 1910, **97**, 2406. *Cf.* Gerrard, *Journ. Physiol.* 1878, **1**, 437.

[6] *Trans. Chem. Soc.* 1911, **99**, 1240

[7] *Arch. Pharm.* 1913, **251**, 357.

[8] *Bull. Jard. Bot. Buitenzorg*, 1919 [iii], **1**, 352 ; 1920 [iii], **2**, 331.

Zephyranthes rosea, Crinum asiaticum,[1] *Crinum giganteum, Crinum pratense, Hymenocallis littoralis, Eucharis grandiflora, Eurycles sylvestris, Amaryllis belladonna,*[2] *Clivia miniata,*[3] *Cooperia Drummondii, Cyrtanthus pallidus,* and *Sprekelia formosissima.*[2] Yamanouchi also found it in *Narcissus Tazetta,*[4] and Gorter suggests it may also be the alkaloid which Robechek[5] found in *Narcissus orientalis.*

The best source of the alkaloid, according to Gorter, is *Crinum giganteum,* from the bulbs of which he obtained from 0·1 to 0·18 per cent. It crystallises in short colourless prisms, m.p. 270° (*decomp.*), $[\alpha]_D^{26} - 120°$ in dry alcohol, sparingly soluble in alcohol, ether or chloroform, insoluble in water, and is best purified by recrystallisation of the hydrochloride. It is slightly alkaline to litmus, but the salts are easily hydrolysed. The hydrochloride, $B.HCl.H_2O$, crystallises in needles, m.p. 206° (*decomp.*), $[\alpha]_D + 43°$; the picrate in yellow leaflets, m.p. 196° from hot water ; and the perchlorate in plates, m.p. 230° (*decomp.*) from warm water. Lycorine contains a methylimino group and a dioxymethylene group, which was found by the resorcinol method. It presents many points of resemblance to hydrastine, *e.g.,* solutions develop an intense blue fluorescence on cautious addition of permanganate, which disappears with excess of the reagent. On catalytic hydrogenation it forms dihydrolycorine, $C_{16}H_{19}O_4N$, small prisms, m.p. 247° (*decomp.*), which no longer gives the blue fluorescence with permanganate. On oxidation with alkaline permanganate it furnishes hydrastic acid (4 : 5-dioxymethylene-*o*-phthalic acid) and oxalic acid. On these grounds Gorter represents it by the following formula :
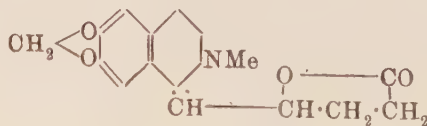
Lycorine (Gorter)

In warm-blooded animals lycorine acts as an emetic, causing eventually collapse and death by paralysis of the central nervous

[1] *Cf.* Greshoff, *Tweede Verslag van het onderzoek naar de plantenstoffen van Nederl. Ind.* (*'s Lands plantentuin, Buitenzorg*).

[2] *Cf.* Fragner's " belamarine," *Berichte*, 1891, **24,** 1498, the existence of which Gorter could not confirm.

[3] *Cf.* Molle, *Jahresberichte Pharm.* 1903, p. 27.

[4] *Arch. Pharm.* 1913, **251,** 357.

[5] *Pharm. Journ.* 1893, p. 183.

system, and it is interesting to note that all the plants in which Gorter found it were already known to possess emetic properties.

Sekisanine, $C_{34}H_{36}O_9N_2$,[1] occurs in the mother liquors from *Lycoris radiata*, from which lycorine has been obtained, and is extracted therefrom by ether. It crystallises in four-sided needles, m.p. 200°. It is moderately soluble in alcohol, but sparingly so in other solvents. The platinichloride melts at 194°.

ALKALOIDS OF *BUPHANE DISTICHA* [2]

From the outer layers of the bulbs of this South African plant Tutin [3] isolated buphanine, lycorine (*see* p. 227), and two unnamed alkaloids.

Buphanine is amorphous and strongly basic, but has not been characterised. It resembles hyoscine in physiological action, but is weaker. On treatment with alcoholic potash it is converted into BUPHANITINE, $C_{23}H_{24}O_6N_2$, which crystallises from alcohol in colourless prisms, containing 1 mol. of the solvent, which is lost at 130°, and the substance then melts at 240°. It is readily soluble in chloroform and moderately so in alcohol or boiling water. The hydrochloride, B.HCl, forms colourless needles, m.p. 265°–268° (*decomp.*), and the methiodide, B.CH₃I, prisms, m.p. 278° (*decomp.*). Buphanitine is physiologically inactive. The other two alkaloids have not been characterised, but one is soluble in water and more basic than the other, and exerts a physiological action similar to those of colchicine and narcissine (lycorine). The less basic alkaloid is a convulsant poison.

ALKALOIDS OF CORYDALIS SPECIES

The following names and formulæ have been assigned to the series of alkaloids found in the roots of *Corydalis tuberosa*. They form three well-marked groups :

I. Corydaline, $C_{22}H_{27}O_4N$; dehydrocorydaline, $C_{22}H_{23}O_4N$; Corybulbine, $C_{21}H_{25}O_4N$; *iso*Corybulbine, $C_{21}H_{25}O_4N$; *d*-Tetrahydropalmatine, $C_{21}H_{25}O_4N$; Corypalmine, $C_{20}H_{23}O_4N$.

[1] Morishima, *Abstr. Chem. Soc.* 1899 [i], 92.
[2] This plant is dealt with here because lycorine is one of its alkaloids. It is not necessarily implied that the other bases present belong to the *iso*quinoline group.
[3] *Trans. Chem. Soc.* 1911, **99**, 1240. *Cf. Arch. exp. Path. Pharm.* 1912, **68**, 333 ; **69**, 314.

II. Corycavine, $C_{22}H_{23}O_6N$; Corycavamine, $C_{21}H_{21}O_5N$; Cory-cavidine, $C_{22}H_{25}O_5N$.

III. Bulbocapnine, $C_{19}H_{19}O_4N$; Corytuberine, $C_{19}H_{21}O_4N$; Corydine, $C_{20}H_{23}O_4N$.

Other Corydalis Alkaloids. Makoshi [1] has obtained from Chinese Corydalis tubers (*C. ambigua*) corydaline, dehydrocorysaline, cory-bulbine, protopine and two other alkaloids : (1) $C_{20}H_{17}O_4N$, a quaternary base giving a hydrochloride, red needles and an auri-chloride, m.p. 280°, and yielding on reduction a colourless tetra-hydro-base, $C_{20}H_{21}O_4N$, m.p. 218°–219° ; and (2) a substance occurring in greyish-white needles, m.p. 197°–199°, resembling, but not identical with, bulbocapnine. The same author isolated from Japanese corydalis roots (*C. vernyi*) only protopine and dehydro-corydaline, but Asahina and Motigase,[2] who state that the tubers examined by Makoshi were derived from *C. decumbens*, obtained from the same plant, in addition to protopine, a non-phenolic alka-loid, m.p. 142° (probably *d*-tetrahydropalmatine (*see* p. 238)), bulbo-capnine and a second phenolic base, m.p. 175°. Protopine is not present in *C. lutea* or *C. nobilis* seeds,[3] and its presence in the roots of *C. tuberosa* is doubtful, though Gadamer [4] obtained it from the sub-aerial parts of this plant along with Haars's alkaloid,[5] m.p. 142°, $[\alpha]_D^{20} + 96 \cdot 8°$ (which Späth, Mosettig and Tröthhandl [6] believe to be *d*-tetrahydropalmatine), and a third alkaloid, $C_{21}H_{21}O_8N$, m.p. 230°, $[\alpha]_D^{20} - 112 \cdot 8°$, a fourth giving a crystalline perchlorate, and a fifth amorphous, yielding only amorphous salts. These five were all non-phenolic. In addition he obtained two phenolic bases closely related to glaucine (p. 243). At the same time Gadamer showed that Gaebel's supposed new alkaloid from *C. tuberosa* roots [7] is a mixture (possibly a molecular combination) of corycavidine with corycavine. According to Heyl,[8] *C. aurea* roots contain protopine and an alkaloid melting at 148°–149°, and *C. solida* (*C. bulbosa*) roots contain two new alkaloids, melting at 145° and 132°–133° respectively.

The following is a summary of a method of isolating the chief

[1] *Arch. Pharm.* 1908, **246**, 381.

[2] *J. Pharm. Soc. Japan*, 1920, 766. *Cf.* Asahina and Fujita, *ibid.* 1920, 763 (*Chem. Soc. Abstr.* 1921 [i], 86).

[3] Schmidt, *Arch. Pharm.* 1908, **246**, 575.

[4] *Ibid.* 1911, **249**, 224.

[5] *Ibid.* 1905, **243**, 154.

[6] *Berichte*, 1923, **56**, 875.

[7] *Arch. Pharm.* 1910, **248**, 207. *Cf.* Späth, *loc. cit.* (6).

[8] *Apoth. Zeit.* 1910, Nos. 5 and 17.

corydalis alkaloids recommended by Gadamer, Ziegenbein, and Wagner.[1] The finely-ground root is exhausted with 94 per cent. alcohol, the solvent removed by distillation, the residue acidified with acetic acid and diluted with water. After cooling, the liquid is filtered and the filtrate shaken with ether. Ammonia is then added and the mixture shaken with successive quantities of ether until alkaloids are no longer removed. The greater part of the ether is distilled off and the residual liquid set aside, when it deposits a mixture of corydaline, bulbocapnine, corycavine, and corybulbine, which are separated in this order by successive extraction of the crystalline mass with boiling alcohol. The mother liquor on concentration to a syrup deposits corydaline. The residue left on completely removing the remaining solvent is converted into the hydrobromides and fractionally precipitated with ammonia, when it yields in turn corydaline, corybulbine, *iso*corybulbine, corycavamine, corycavine, corydine and bulbocapnine. The ammoniacal aqueous solution still contains some corytuberine, which is recovered by evaporating the liquid to a syrup, adding ammonia and extracting with chloroform. The crude corydaline is purified by converting it into the hydrochloride and adding dilute soda to an aqueous solution of the latter, when corydaline with some corycavine is precipitated, whilst bulbocapnine passes into the alkaline solution and can be regenerated by carbon dioxide. The two former alkaloids are best separated by repeated crystallisation from absolute alcohol, corycavine accumulating in the earlier and corydaline in the later fractions. Advantage may also be taken of the greater solubility of corydaline hydrochloride in dilute hydrochloric acid over that of the corycavine salt.

The arrangement of these alkaloids into three groups is due to Gadamer, Ziegenbein and Wagner. Group I. consists of weakly basic alkaloids, which are readily oxidised by iodine to berberine-like compounds. Group II. includes stronger bases, which are attacked by iodine solution. Group III. comprises the strongest bases of the series ; these are oxidised by iodine and contain free phenolic hydroxyl groups.

Group I.

Corydaline, $C_{22}H_{27}O_4N$. This, the principal alkaloid of *Corydalis* root, was discovered in 1826 by Wackenroder,[2] and was subsequently examined by several investigators, but not in a pure state until

[1] *Arch. Pharm.* 1902, **240**, 19.
[2] *Berz. Jahr.* 1826, **7**, 220.

1866, when Wicke [1] analysed well-crystallised salts of the alkaloid and assigned to it the formula $C_{18}H_{19}O_4N$. Birsmann [2] changed this to $C_{22}H_{23}O_4N$, which Dobbie and Lauder in turn altered to $C_{22}H_{29}O_4N$, but Freund and Josephi found that the alkaloid was better represented by the formula $C_{22}H_{27}O_4N$, and this is now generally adopted. [3]

Corydaline crystallises from alcohol in colourless, short, six-sided prisms, m.p. 135°, $[\alpha]_D^{20} + 300°$ (in chloroform), is sparingly soluble in cold alcohol, but dissolves readily on warming, is easily soluble in ether or chloroform, insoluble in water or alkalis. Exposed to air, it gradually oxidises to yellow dehydrocorydaline. It forms well-crystallised salts of which the hydriodide, B.HI, obtained by double decomposition of the hydrochloride with potassium iodide forms pale yellow prisms of indefinite melting-point; the nitrate, $B.HNO_3$, crystallises from alcohol in tablets, m.p. 198°; the hydrochloride, $B.HCl.2H_2O$, columnar crystals, m.p. 206°–207°; the aurichloride crystallises from dilute alcoholic hydrochloric acid in orange-coloured needles, m.p. 207°. The platinichloride forms brown crystals, m.p. 227°. The most characteristic salt is corydaline ethyl sulphate, $B.C_2H_5HSO_4.H_2O$, which crystallises in large prisms, m.p. 152·5°.

CONSTITUTION. Corydaline contains four methoxyl groups. It reacts with methyl iodide, forming corydaline methiodide, and therefore contains a tertiary nitrogen atom. Further insight into the constitution of the alkaloid has been obtained principally by the study of its oxidation by permanganate and similar agents, by which means the alkaloid may be gradually broken down, as shown in the tabular arrangement on p. 233. [4]

The ultimate products of oxidation are therefore pyridine-2 : 3 : 4 : 6-tetracarboxylic, hemipinic, and *meta*hemipinic acids, furnishing evidence of the existence in the molecular complex of the alkaloid of two benzene rings and at least one pyridine ring.

Methylpyridinetricarboxylic acid, $C_9H_7O_6N$. This substance, obtained [5] by oxidising corydic acid or corydilic acid with permanganate, crystallises in prisms, m.p. 208°, furnishes well-crystal-

[1] *Annalen*, 1866, **137**, 274.

[2] *Inaug. Diss. Dorpat.* 1888.

[3] *Trans. Chem. Soc.* 1892, **61**, 244 ; *Annalen*, 1893, **277, 1.** *Cf.* Ziegenbein, *Arch. Pharm.* 1896, **234,** 492 ; Martindale, *ibid.* 1898, **236,** 214.

[4] Dobbie and Lauder, *Trans. Chem. Soc.* 1902, **81**, 145 ; 1903, **83**, 605. *Cf.* Haars, *Arch. Pharm.* 1905, **243,** 165.

[5] Dobbie and Marsden, *Trans. Chem. Soc.* 1897, **71**, 657.

Corydaline, $C_{22}H_{27}O_4N$

Oxidation by permanganate   Oxidation by dilute nitric acid

Corydaldine,   m-Hemipinic acid   Dehydrocorydaline,
$C_{11}H_{13}O_3N$ $C_{22}H_{23}O_4N$

Hemipinic acid   Corydic acid,   Methylpyridine-
                        $C_{18}H_{17}O_6N$ tricarboxylic acid,
                                            $C_9H_7O_6N$

m-Hemipinic acid

Further oxidation by permanganate

Corydilic acid,   m-Hemipinic   Methylpyridine-
$C_{17}H_{15}O_8N$ acid   tricarboxylic acid

m-Hemipinic acid   Methylpyridine-   Pyridine-2 : 3 : 4 : 6-tetracarboxylic
                        tricarboxylic acid   acid, $C_9H_5O_8N$

lised salts, and when dissolved in potash solution and treated with permanganate is oxidised to pyridine-2 : 3 : 4 : 6-tetracarboxylic acid. The formation of this acid makes it possible to assign a position to the methyl group of the methylpyridinetricarboxylic acid.[1] Assuming that corydaline contains an *iso*quinoline nucleus, then, in the opening of the pyridine ring of this complex by oxidation, there must be formed a carboxyl group in the 6-position (*see* I *and* II, p. 234) ; the two remaining carboxylic groups are probably formed by the destruction of a ring joined to the pyridine ring by the carbon atoms 3 : 4- or 4 : 5. The methyl group must, therefore, be in position 2. These considerations led Dobbie and Lauder to formulate the acid as 2-methylpyridine-3 : 4 : 6-tricarboxylic acid, but Lawson, Perkin, and Robinson have recently synthesised the acid of this constitution and shown it to be different from Dobbie and Lauder's acid.

Corydilic acid, $C_{17}H_{15}O_8N$. This tribasic acid crystallises from alcohol in needles with $2H_2O$, m.p. 228°, is formed by the oxidation of corydic acid with permanganate, and is itself oxidised by this

[1] Dobbie and Lauder, *Trans. Chem. Soc.* 1902, **81**, 152.

reagent to methylpyridinetricarboxylic and *meta*hemipinic acids. It contains two methoxyl groups.[1] On these grounds Dobbie and Lauder [2] assigned to this acid formula I, which Haars [3] modified to formula II, since it gave a methiodide and appeared to be a tertiary base.

C.COOH
C   C.COOH
CH C   C.CH$_3$
CH$_3$O.C   C   NH
CH$_3$O.C   C.COOH
CH

(I)
Corydilic acid
(Dobbie and Lauder)

C.COOH
HC   C.COOH
CH C   C.CH$_3$
CH$_3$O.C   C   N
CH$_3$O.C   C.COOH
CH
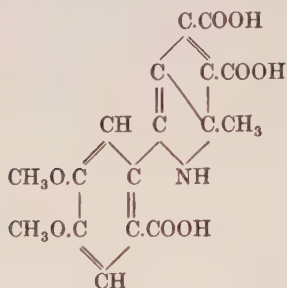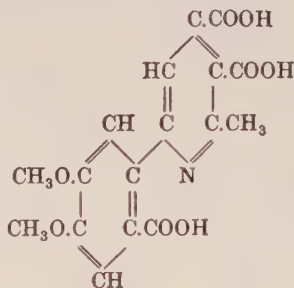
(II)
Corydilic acid
(Haars)

Corydic acid, $C_{18}H_{17}O_6N$, formed by the oxidation of dehydro-corydaline with dilute nitric acid, crystallises in yellow leaflets with $2H_2O$, m.p. 218°, or with $1H_2O$, m.p. 224°, behaves as a dibasic acid, contains two methoxyl groups and a tertiary nitrogen atom. When oxidised by permanganate it furnishes corydilic acid. Dobbie and Lauder assigned formula III to corydic acid, which Haars modified as shown in formula IV, since in his experiments the dimethyl ester formed salts as a quaternary base :

C.COOH
C   C.COOH
CH C   C.CH$_3$
CH$_3$O.C   C   N
CH$_3$O.C   C   CH$_2$
CH   CH$_2$
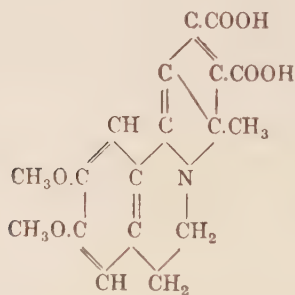
III
Corydic acid (Dobbie and Lauder)

C.COOH
HC   C.CO—O—
CH C   C.CH$_3$
CH$_3$O.C   C   N
CH$_3$O.C   C   CH$_2$
CH   CH$_2$
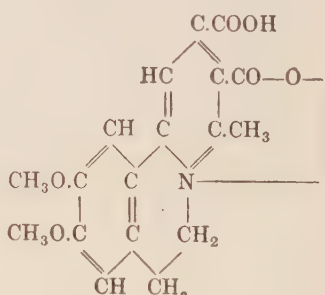
IV
Corydic acid (Haars)

[1] Dobbie and Marsden, *Trans. Chem. Soc.* 1897, **71**, 657.   *Cf.* 1902, **81**, 148.
[2] Dobbie and Lauder, *Trans. Chem. Soc.* 1902, **81**, 152.
[3] *Arch. Pharm.* 1905, **243**, 165.

Corydaldine, $C_{11}H_{13}O_3N$, obtained by oxidising corydaline with permanganate, forms prismatic crystals, m.p. 175°, and reacts with nitrous acid, giving nitrosocorydaldine, m.p. 185°, which when warmed with sodium hydroxide solution loses nitrogen and passes into the lactone of hydroxyethylveratric acid (II). With hydrochloric acid at 150° the latter furnishes a phenol, giving reactions similar to those of the catechol derivative obtained by Perkin (*see* p. 212) in the same way from hydroxyethylpiperonylcarboxylic anhydride, with which it is probably identical. Formula I was, therefore, assigned to corydaldine.[1]

(I)
Corydaldine
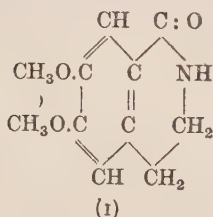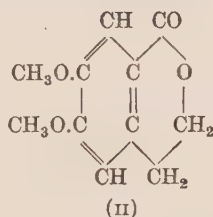
(II)
Hydroxyethylveratric lactone

Dehydrocorydaline, $C_{22}H_{23}O_4N$. This alkaloid occurs in the roots of *Corydalis tuberosa*, *C. vernyi*, *C. ambigua* and *C. solida*, and is also formed by the gentle oxidation of corydaline.[2] It is a yellowish crystalline powder, m.p. 112°–113° (*decomp.*). The salts are crystalline ; the hydrochloride, $B.HCl.4H_2O$, yellow leaflets ; aurichloride, $B.HAuCl_4$, red-brown needles, m.p. 219° ; the hydriodide, $B.HI.2H_2O$, small yellow needles. Like berberine, it unites with one molecule of chloroform to form a colourless crystalline compound, m.p. 154°.

Dehydrocorydaline contains four methoxyl groups and gives a crystalline oxime, m.p. 165°. On reduction it furnishes two isomerides of corydaline, m.p. 135° and m.p. 158°–159°, the latter (*r*-mesocorydaline) by crystallisation of the *d*-camphorsulphonate can be partially separated into *d*- and *l*-forms, the *d*-form of which is not identical with natural corydaline.[3] The second isomeride,

[1] Dobbie and Lauder, *Trans. Chem. Soc.* 1899, **75**, 670.

[2] Schmidt, *Arch. Pharm.* 1896, **234**, 489 ; Haars, *ibid.* 1905, **243**, 165. *Cf.* Dobbie and Marsden, *Trans. Chem. Soc.* 1897, **71**, 659.

[3] Gadamer and Wagner, *Arch. Pharm.* 1902, **240**, 19. *Cf.* Haars, 1905, **243**, 165.

m.p. 135° (r-corydaline), has not itself been deracemised, but the sulphonic acid has been separated into the d- and l-components by crystallisation of the brucine salt, and the former is identical with the similar sulphonic acid of natural corydaline, so that the inactive corydaline, m.p. 135°, must be regarded as r-corydaline.[1] The formula I assigned to dehydrocorydaline salts (X = acid radicle) is mainly due to Dobbie and Lauder,[2] but was slightly modified by
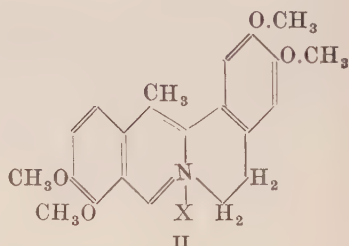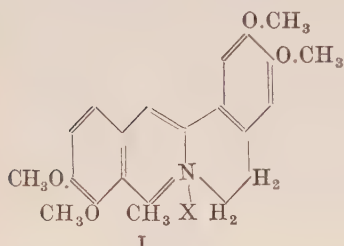
Haars[3]; and has recently been further modified to formula II by Gadamer and Bruchhaüsen[4] on the following grounds : (1) The new formula accounts equally well for the formation of two racemic modifications of corydaline by reduction of dehydrocorydaline ; (2) it explains why α-methyltetrahydropalmatine is not identical with either of the racemic forms of corydaline (cf. p. 226) ; and (3) it accounts for the simultaneous formation of oxydehydro-corydaline, $C_{22}H_{23}O_5N$, m.p. 228°, and dihydrodehydrocorydaline, $C_{22}H_{25}O_4N$, when dehydrocorydaline acetate is treated with 30 per cent. caustic soda solution just as berberine (p. 215) is converted in like manner into oxyberberine and dihydroanhydro-berberine.

Dehydrocorydaline exhibits many analogies with berberine (p. 208) ; thus both are yellow and both are easily reduced, forming the colourless alkaloids, corydaline and tetrahydroanhydroberberine (p. 217) respectively. On the basis of the results summarised above, Dobbie and Lauder[5] assigned the following formula to corydaline :

[1] Gadamer and Klee, *Arch. Pharm.* 1916, **254,** 295.

[2] *Trans. Chem. Soc.* 1902, **81,** 148. *Cf.* Gadamer, *Arch. Pharm.* 1902, **240,** 43.

[3] Gadamer and Wagner, *Arch. Pharm.* 1902, **240,** 19. *Cf.* Haars, 1905, **243,** 165.

[4] *Arch. Pharm.* 1921, **259,** 246.

[5] *Loc. cit.*

```
            CH                                      CH
           ╱╲                                      ╱╲
         CH   C.OCH₃                             CH   C.OCH₃
         │ ɪ ‖                                   │ ɪ ‖
         C    C.OCH₃                             C    C.OCH₃
            ╱╲                                      ╱╲
         CH₂  C                                   CH₂  C
         │ ɪɪ │                                   │ ɪɪ │
       CH   CH   CH.CH₃                         CH   CH   CH₂
      ╱╲  ╱╲  ╱                            ╱╲  ╱╲  ╱
CH₃O.C   C    N                      O—C    C    N
    │ ɪv ‖ ɪɪɪ │                  CH₂⟨ │ ɪv ‖ ɪɪɪ │
CH₃O.C   C    CH₂                    O—C    C    CH₂
      ╲╱  ╲╱                            ╲╱  ╲╱
      CH   CH₂                          CH   CH₂
```
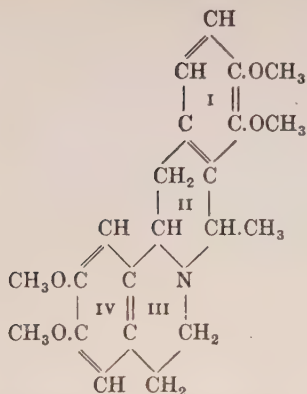
Corydaline (Dobbie and Lauder)   *Tetrahydroanhydroberberine*
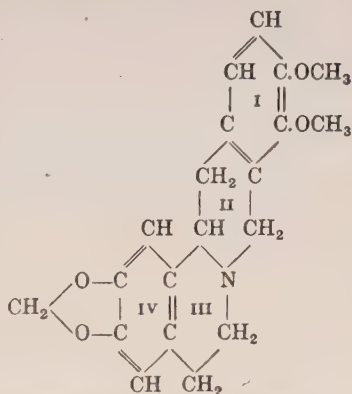
which differs from that of tetrahydroanhydroberberine only in having two methoxyl groups in place of a dioxymethylene group in ring ɪv, and a methyl group substituted for a hydrogen atom in ring ɪɪ. Gadamer and von Bruchhaüsen [1] have suggested, on the grounds already referred to in connection with dehydrocorydaline (p. 236), that the arrangement in ring ɪɪ is as follows:

$$\begin{array}{c} —C—CHMe.CH.C:\\ \| \quad _4 \qquad ^3| \\ —C—CH_2—N.CH_2. \end{array}$$

and the validity of this suggestion has been demonstrated by Bruchhaüsen's synthesis [2] of *r*-corydaline from palmatine-acetone by the action of methyl iodide and reduction of the methylated product. Freund and Speyer [3] have shown that under these conditions it is carbon atom (4) that is methylated in preference to the *N* in ring ɪɪ; berberine, *e.g.*, yields 4-methyldihydroberberine, which can then be reduced to 4-methyltetrahydroberberine.

Corybulbine, $C_{21}H_{25}O_4N$. This alkaloid was isolated from commercial corydaline by Freund and Josephi.[4] It crystallises from boiling absolute alcohol in colourless needles, m.p. 238°, $[\alpha]_D + 303\cdot3$ (in chloroform), is insoluble in water, slightly soluble in methyl alcohol or ether, readily soluble in chloroform, acetone or hot benzene. The hydrochloride, B.HCl, is slightly soluble in hot water, from which it crystallises in yellowish prismatic crystals,

[1] *Arch. Pharm.* 1922, **259**, 245.   *Cf.* Späth and Lang, *Berichte*, 1921, **54ʙ**, 3074; and Lawson, Perkin, and Robinson, *Trans. Chem. Soc.* 1924, **125**, 632.

[2] *Arch. Pharm.* 1923, **260**, 31.

[3] *Annalen*, 1913, **397**, 1; 1915, **409**, 188.

[4] *Annalen*, 1893, **277**, 1.

m.p. 245°–250° (*decomp.*). The platinichloride and aurichloride are amorphous. When treated with iodine, corybulbine is oxidised to dehydrocorybulbine, $C_{21}H_{21}O_4N$, m.p. 210°–211°, and the latter on reduction regenerates an optically inactive corybulbine,[1] m.p. 220°–222°. When heated with methyl iodide in presence of potash, corybulbine is converted into corydaline, from which it differs only in possessing a hydroxyl in place of a methoxyl group. Evidence of the existence of the hydroxyl group is found in the solubility of the alkaloid in alkalis and in the formation of acetylcorybulbine, m.p. 160°.

The position of the hydroxyl group has not been ascertained with certainty, but, since the alkaloid does not give corydic acid by oxidation with nitric acid, Dobbie, Lauder and Paliatseas [2] suggest that it must occur in ring IV (*see* corydaline formula, p. 237).

*iso*Corybulbine, $C_{21}H_{25}O_4N$, was first obtained by Gadamer and Ziegenbein,[3] and was subsequently examined by Bruns.[4] It separates from alcohol in colourless, voluminous leaflets, m.p. 179°–180°, $[\alpha]_D + 299 \cdot 8°$ (in chloroform), and closely resembles corybulbine. It contains three methoxyl groups, and on oxidation with iodine yields dehydro*iso*corybulbine ; the hydriodide of the latter is reduced by zinc and sulphuric acid to *i-iso*corybulbine, m.p. 165°–167°. Bruns [4] suggests that since corydaline, corybulbine and *iso*corybulbine all yield the same *apo*corydaline when boiled with hydriodic acid, the only difference between the two latter must be due to the relative positions of the methoxyl and hydroxyl groups,

d-Tetrahydropalmatine, $C_{21}H_{25}O_4N$ (*cf.* p. 225). This alkaloid was isolated by Späth, Mosettig and Tröthandl [5] from *C. tuberosa* roots grown near Vienna in 1922. It is crystalline, melts at 142°, has $[\alpha]_D^{17°} + 292 \cdot 5°$ (in alcohol), and, though colourless, develops a yellow tint on exposure to air. The crystals are triboluminescent. The hydrochloride, B.HCl, is sparingly soluble in water. On oxidation with iodine in alcohol at 100°, it yields the iodide of a yellow quaternary base, m.p. 238°–239° (*decomp.*), probably palmatine iodide (p. 225), since with magnesium methyl iodide it furnished an α-methyldihydro-base, which on reduction gave *dl*-α-methyltetrahydropalmatine already prepared by Späth and Lang in an attempt to convert palmatine into corydaline (p. 226).

[1] Bruns, *Arch. Pharm.* 1901, **239**, 39 ; 1903, **241**, 634.
[2] *Trans. Chem. Soc.* 1901, **79**, 87.
[3] *Arch. Pharm.* 1902, **240**, 19.
[4] *Ibid.* 1903, **241**, 634.
[5] *Berichte*, 1923, **56**, 877.

Efforts to confirm the view that the alkaloid is d-tetrahydropalmatine by resolution of dl-tetrahydropalmatine were unsuccessful. The authors point out that alkaloids melting at temperatures near 142° have been isolated by Haars,[1a] Gaebel[1b] and Heyl,[1c] which may also prove to be d-tetrahydropalmatine.

Corypalmine, $C_{20}H_{23}O_4N$. This alkaloid, obtained by Späth, Mosettig and Tröthandl,[2] along with the foregoing, forms minute colourless crystals, m.p. 235°–236°, $[\alpha]_D^{16} + 280°$ (in chloroform), and on methylation with nitrosomethylurethane, in presence of sodium hydroxide, yields d-tetrahydropalmatine, which is, therefore, the monomethyl ether of corypalmine. The position of the hydroxyl group in the latter is not yet determined.

Group II

Corycavine, $C_{23}H_{23}O_6N$. This alkaloid was isolated by Freund and Josephi[3] from corydalis roots, and was subsequently examined by Gadamer, Ziegenbein and Wagner,[4] and by Gaebel.[5] It crystallises from hot absolute alcohol in rhombic tablets, m.p. 218°–219°, $[\alpha]_D$ 0°, and is insoluble in water, cold alcohol or alkalis. The hydrochloride, $B.HCl.H_2O$, forms needles melting at 219°; the hydriodide, $B.HI.H_2O$, small yellowish needles, m.p. 236°; the platinichloride, $(B.HCl)_2.PtCl_4$, yellowish crystals, m.p. 214° (*decomp.*); the aurichloride, $B.HAuCl_4$, has m.p. 178°–179° (*decomp.*). Corycavine forms a methiodide, rhombic tablets, m.p. 218°, and behaves as a tertiary base containing : NCH_3. It contains two dioxymethylene groups,[6] but no hydroxyl or methoxyl. According to Gaebel,[6] corycavine on exhaustive methylation yields finally trimethylamine and an amorphous non-nitrogenous substance, and so far no useful results have been obtained in oxidation experiments.

Corycavamine, $C_{21}H_{21}O_5N$, was first obtained by Gadamer, Ziegenbein and Wagner,[4] and is best purified by recrystallisation of the nitrate from boiling water. The free base forms rhombic columns, m.p. 149°, $[\alpha]_D^{20} + 166.6°$ in chloroform. It contains no

[1] *Arch. Pharm.* (a) 1905, **243**, 162; (b) 1910, **248**, 220; (c) 1903, **241**, 318.

[2] *Berichte,* 1923, **56**, 877.

[3] *Annalen,* 1893, **277**, 1.

[4] *Arch. Pharm.* 1902, **240**, 19.

[5] *Arch. Pharm.* 1910, **248**, 207.

[6] Gadamer and Bruchhaüsen, *ibid.* 1921, **259**, 247.

methoxyl groups, but two dioxymethylene groups. The hydro-bromide and hydriodide crystallise in needles, but the platinichloride is amorphous. When warmed with acetic anhydride or heated alone at $180°$, it is converted into an optically inactive modification, m.p. $213°–214°$, which resembles cryptopine (p. 298), but is not identical with it.

Corycavidine, $C_{22}H_{25}O_5N$, was described by Gadamer.[1] It crystallises from hot chloroform with one molecule of the solvent, melts at $212°–213°$, has $[\alpha]_D^{20} + 203·1°$ (in chloroform), and yields a crystalline hydrochloride and nitrate, and an amorphous red aurichloride, m.p. $170°$ (*decomp.*). It contains two methoxyl groups and a : NMe group, and appears to be corycavamine in which one dioxymethylene group is replaced by two methoxyls. Like cory-cavamine, when heated at $209°$, it is converted into an inactive modification, m.p. $193°–195°$. On exhaustive methylation it yields in two stages trimethylamine and a neutral substance.

Group III

Bulbocapnine, $C_{19}H_{19}O_4N$. This alkaloid, first isolated by Freund and Josephi,[2] crystallises from hot, dry alcohol in rhombic needles, m.p. $199°$, $[\alpha]_D + 237·1°$ (in chloroform), is insoluble in water, readily soluble in chloroform or alkalis (developing a green coloration), but is precipitated from solution in the latter by excess of carbon dioxide. The hydrochloride forms needles, m.p. $270°$ (*approx.*, *decomp.*) ; the platinichloride is crystalline, m.p. $200°$ and $230°$ (*decomp.*). The methiodide, m.p. $257°$, forms brilliant needles. The base was formerly regarded as a partially demethylated de-hydrocorydaline, the latter being supposed to have the formula, $C_{22}H_{25}O_4N$, thus :

$C_{18}H_{13}(OCH_3)_4N$	$C_{18}H_{13}(OH)_3(OCH_3)N$
Dehydrocorydaline	*Bulbocapnine*
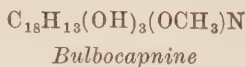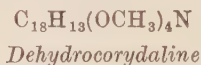
but the observations of Gadamer and Ziegenbein[3] and of Dobbie and Lauder,[4] indicated that such a relationship did not exist, and this was confirmed by Gadamer and Kuntze,[5] who showed that bulbocapnine contained one methoxyl, one hydroxyl, and a

[1] *Arch. Pharm.* 1911, **249**, 30.
[2] *Annalen*, 1893, **277**, 10.
[3] *Arch. Pharm.* 1902, **240**, 81.
[4] *Trans. Chem. Soc.* 1903, **83**, 612.
[5] *Arch. Pharm.* 1911, **249**, 503, 598.

dioxymethylene group. On exhaustive methylation it yielded trimethylamine and 3 : 4-dimethoxy-5 : 6-methylenedioxy-8-vinyl-phenanthrene, and on these grounds formula I (p. 242) was assigned to it.

Corydine, $C_{20}H_{23}O_4N$, was first prepared by Merck [1] and was subsequently examined by Gadamer and collaborators.[2] It crystallises from alcohol with $\frac{1}{2}C_2H_5OH$, m.p. 124°–125°, or 149° (*dry*) $[\alpha]_D^{20} + 204\cdot3°$ (in chloroform), and is readily soluble in alcohol or chloroform. It contains three methoxyl groups and one hydroxyl group, and on oxidation with iodine yields dehydrocorydine hydriodide, $C_{20}H_{19}O_4N . HI$. This, on reduction, yields *dl*-corydine, m.p. 165°–167°, which on recrystallisation of the *d*-tartrate yields *l*-corydine $[\alpha]_D^{20} - 206\cdot2°$ in chloroform. Corytuberine (*see below*), on methylation with diazomethane, yields a mixture of corydine and *iso*corydine, so that these two alkaloids are monomethyl ethers of corytuberine as shown by the formula on p. 242.

*iso***Corydine,** $C_{20}H_{23}O_4N$, is obtained along with corydine (*see above*) when corytuberine is methylated with diazomethane or methyl sulphate.[3] It crystallises in glistening four-sided tablets, m.p. 185° $[\alpha]_D^{20} + 195\cdot3°$ in chloroform, and yields a methiodide, m.p. 213°–214° (*decomp.*), $[\alpha]_D^{20} + 143\cdot3°$.

Corytuberine, $C_{19}H_{21}O_4N . 5H_2O$. This alkaloid was obtained by Dobbie and Lauder [4] from commercial corydaline by exhausting the latter with boiling water. It crystallises in silky needles, m.p. 240° (*decomp.*), $[\alpha]_D^{20} + 282\cdot65°$ (in alcohol), is insoluble in benzene or ether, and sparingly in chloroform, but dissolves readily in alkalis, the solution darkening in air. The salts are crystalline. The base forms a crystalline methiodide, contains two methoxyl and two phenolic hydroxyl groups.[5] On methylation it yields a mixture of corydine and *iso*corydine (*see above*). On exhaustive methylation, corytuberine yields eventually trimethylamine and 3 : 4 : 5 : 6-tetramethoxy-8-vinylphenanthrene, m.p. 69°.

It is clear from these results that bulbocapnine, corydine, *iso*corydine, and corytuberine, are all closely related, and Gadamer,[6]

[1] *Chem. Soc. Abstr.* 1893 [i], 492.

[2] *Arch. Pharm.* 1902, **240,** 81 ; 1911, **249,** 503, 669.

[3] Gadamer, *Arch. Pharm.* 1911, **249,** 485, 669.

[4] *Trans. Chem. Soc.* 1893, **63,** 485. *Cf.* Gadamer, *Arch. Pharm.* 1911, **249,** 532.

[5] Gadamer, Ziegenbein, and Wagner, *Arch. Pharm.* 1902, **240,** 81.

[6] *Ibid.* 1911, **249,** 503, 641 ; 1921, **259,** 135.

on the basis of these investigations, has assigned to them the following formulæ :

CH   CH$_2$ N.CH$_3$
CH   C   CH   CH$_2$
CH$_3$O.C   C   C   CH$_2$
HO.C   C   C
O—C   CH
H$_2$C—O—C

Bulbocapnine

CH   CH$_2$ N.CH$_3$
CH   C   CH   CH$_2$
HO.C   C   C   CH$_2$
HO.C   C   C
CH$_3$O.C   CH
C.OCH$_3$

Corytuberine

CH   CH$_2$ N.CH$_3$
CH   C   CH   CH$_2$
HO.C   C   C   CH$_2$
CH$_3$O.C   C   C
CH$_3$O.C   CH
CH$_3$O.C

Corydine [1]
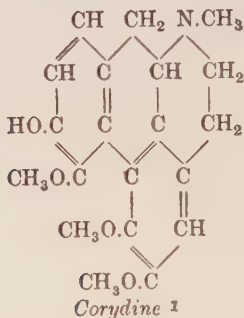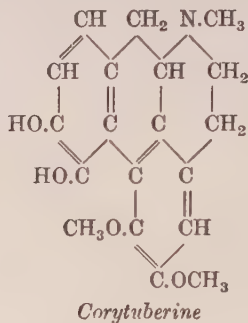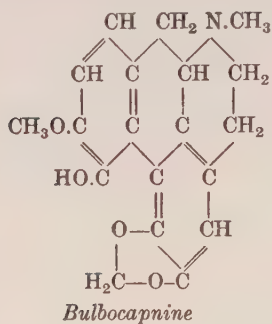
in which it will be seen that the reduced pyridine ring II forms a partially reduced quinoline with ring III, and a less reduced *iso*-quinoline with ring I, and this essential difference in structure from the corydaline group is reflected in the difference in their physiological action.　The three homocyclic rings together form the phenanthrene nucleus, which is also present in apomorphine, and corytuberine in particular resembles apomorphine in physiological action.

Physiological Action.　Peters [2] has shown that the physiological action of the Corydalis alkaloids can be correlated with their division into the three chemical groups already referred to.　All the alkaloids except corytuberine produce in frogs narcosis similar to that induced by morphine, but while the corydaline sub-group

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[1] *iso*Corydine differs from corydine merely in the interchange of hydroxyl and methoxyl in positions 3 and 4 in the phenanthrene nucleus.

[2] *Inaug. Diss. Marburg* 1904 ; *Arch. Pharm.* 1905, **243,** 113 ; and *Arch. Exp. Path. Pharm.* 1903, **51,** 130.

produces paralysis of the spinal cord, the corycavine sub-group stimulates the motor centres and finally paralyses the spinal cord, and bulbocapnine and its allies cause increased reflex excitability, followed by paralysis of the spinal cord. All three sub-groups cause weakening of the action of the heart in frogs.

In warm-blooded animals the effects of the three sub-groups are less clearly differentiated ; the corydaline sub-group (corydaline, corybulbine and *iso*corybulbine) produce little or no narcosis, weaken the action of the heart and lessen circulation. The corycavine sub-group (corycavine and corycavamine) cause increased secretion of tears and saliva, epileptiform convulsions without increased reflex excitability and by central action lead to increased blood-pressure. Of the bulbocapnine sub-group (bulbocapnine, corydine) corydine produces slight narcosis, bulbocapnine an almost cataleptic condition, especially in cats.[1] Both cause increased secretion of tears and saliva, and corydine produces emesis. Both retard respiration, and corydine produces by central action a rise in blood-pressure. Corytuberine, which chemically also belongs to this sub-group, has a different action ; it causes tonic convulsions with slight increase of reflex excitability, increased secretion of tears and saliva, emesis, slows the heart's action by vagus stimulation and increases the rate of respiration.

ALKALOIDS OF *GLAUCIUM FLAVUM*

The stem, leaves and flowers of this plant were examined by R. Fischer,[2] and found to contain glaucine and protopine (p. 302), whilst the root contained protopine, traces of chelerythrine (p. 247) and sanguinarine (p. 252). Glaucine is best separated from protopine by extracting the mixture of hydrochlorides with chloroform in which the glaucine salt is soluble.

Glaucine, $C_{21}H_{25}O_4N$, was obtained by Probst [3] from *G. flavum* (*G. luteum*), but was first prepared in a pure state by R. Fischer.[2] It crystallises in yellow, rhombic prisms, m.p. 119°–120°, $[\alpha]_D + 113\cdot3°$ (115·4°) [4] in alcohol, is readily soluble in alcohol or chloroform, fairly so in ether, and sparingly so in benzene or hot water. The hydrochloride, $B.HCl.3H_2O$, forms colourless crystals, and the

[1] de Jong, *Klin. Woch.* April 1st, 1922, p. 684.
[2] *Arch. Pharm.* 1901, **239,** 426.
[3] *Annalen,* **31,** 241.
[4] Gadamer, *Arch. Pharm.* 1911, **249,** 680.   *Cf.* Pschorr, *Berichte,* 1904, **37,** 1926.

hydrobromide, B.HBr, pale pink crystals, m.p. 235°. The alkaloid itself is tasteless, but the salts are bitter. Glaucine dissolves in sulphuric acid, forming a colourless liquid which becomes bright blue after some hours. If the mixture is heated it rapidly becomes violet. Nitric acid gives a transient green tint ; Fröhde's reagent (sulphomolybdic acid in sulphuric acid) yields a green passing into blue. Glaucine behaves as a tertiary base and contains four methoxyl groups. It was synthesised by Gadamer [1] by treating a diazotised solution of N-methyltetrahydroaminopapaverine (amino-laudanosine (I)) with copper powder, when phenanthreno-N-methyltetrahydropapaverine, which proved to be dl-glaucine (II) was formed, thus :

Glaucine (Gadamer)
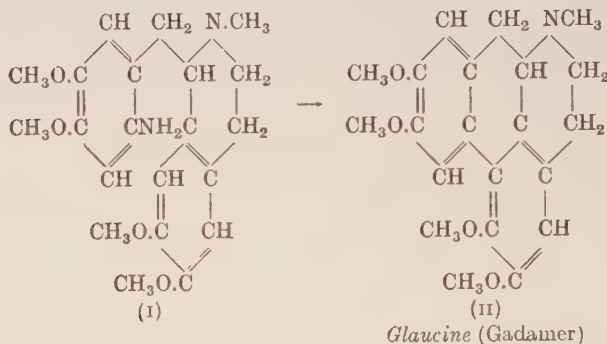
The dl-glaucine thus prepared has m.p. 137°–139°, and on recrystallisation of the d- and l-hydrogen tartrates furnishes the corresponding salts of d- and l-glaucine, from which the free bases are obtainable, the d-glaucine thus produced being identical with the natural alkaloid, which is thus shown to be closely allied to the bulbocapnine group of alkaloids (p. 240) like its isomeride *iso*glaucine (p. 245). The glaucidine of *Papaver orientale* (p. 310), is said to be closely related to glaucine.[2]

Glaucine exhibits narcotic properties, depresses the action of the heart, and also shows some tetanising action.

ALKALOID OF *LITSEA CUBEBA*

Laurotetanine, $C_{19}H_{21}O_4N.H_2O$. This alkaloid was first isolated by Greshoff [3] from *Litsea chrysocoma*, who also found it in a number

[1] Gadamer, *Arch. Pharm.* 1911, **249**, 680. *Cf.* Pschorr, *Berichte*, 1904, **37**, 1926.

[2] Gadamer, *ibid.* 1914, **252**, 274.

[3] *Berichte*, 1890, **23**, 3537.

of other plants of the same natural order (Lauraceæ), and subsequently by Filippo [1] from *Litsea citrata*, and was recently obtained from *L. cubeba* and examined by Gorter.[2]

It crystallises from acetone with one molecule of water and then melts at 125°, but can be dehydrated at 80° over phosphorus pentoxide. It is dextrorotatory, $[\alpha]_D^{25} + 98.5°$, colourless, but becomes yellow on exposure to air, behaves as a phenolic base and yields a phenylthiocarbimide, $NHPh.CS.NH.C_{19}H_{20}O_4N$, m.p. 211°–212°. The hydrochloride ($+ 6H_2O$), hydrobromide ($+ 6H_2O$), hydriodide ($+ 5H_2O$), sulphate, $B_2.H_2SO_4$ ($+ 12$ or $5H_2O$), and the picrate ($+ 1.5 H_2O$), m.p. 148°, are all crystalline. Dibenzoyllaurotetanine has m.p. 169°–170°. With nitrosodimethylurethane the base yields a monomethyl ether, $C_{20}H_{23}O_4N$ (amorphous, but yielding crystalline salts), and with diazomethane *N*-methyllaurotetanine methyl ether, $C_{21}H_{25}O_4N.3H_2O$, m.p. 63°, $[\alpha]_D^{27} + 109°$ which sublimes unchanged *in vacuo*, and since it resembles glaucine in optical rotation, colour reactions and pharmacological action, has been named *iso*glaucine. The salts are crystalline; hydrochloride, B.HCl ($+ 2$ or $5H_2O$), m.p. 239° (*dry*), hydrobromide, m.p. 252°. On the above grounds Gorter assigns the following formula to *iso*glaucine, since this accounts for the similarity to
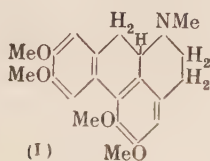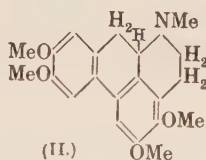
(I) *Glaucine*   (II.) iso*Glaucine*

glaucine in pharmacological action and colour reactions, and is the only alternative to the glaucine formula which accounts for the fact that on oxidation with alkaline permanganate, laurotetanine yields 1 : 2-dimethoxybenzene-3 : 4 : 5-tricarboxylic acid, m.p. 165°: glaucine should also yield this acid.

The HO— group in laurotetanine is believed to replace one of the methoxyl groups in the ring on the extreme left of the formula.

In frogs, laurotetanine acts as a tetanising poison, but is less active than strychnine.

[1] *Arch. Pharm.* 1898, **236**, 601.
[2] *Bull. Jard. bot. Buitenzorg*, 1921 [iii], **3**, 180 (*Chem. Soc. Abstr.* 1921 [i], 587).

ALKALOIDS OF *DICENTRA* SPECIES

The roots of four species of *Dicentra* (*Diclytra*) have been examined and shown to contain the following alkaloids :

D. Cucullaria. Protopine and two alkaloids, provisionally termed *c* and *d*. Alkaloid *c* crystallises in rosettes of needles, m.p. 230°–231° (*decomp.*), is very sparingly soluble in alcohol and slightly in chloroform. It is colourless, but rapidly becomes yellow in the light. Alkaloid *d* forms granular crystals, m.p. 215°, and is fairly soluble in alcohol.[1]

D. formosa. Protopine and at least two other alkaloids, which were separated by fractional crystallisation of the hydrobromides from dilute alcohol.[2] The one giving the less soluble hydrobromide had m.p. 168·5°–169°, was shown later by Asahina to be dicentrine,[3] and the other, m.p. 142·5°, may be *d*-tetrahydropalmatine (*cf.* p. 238).

D. pusilla. Protopine and dicentrine.[3]

D. spectabilis contains protopine,[4] sanguinarine, and a third alkaloid, m.p. 142°, giving a sparingly soluble perchlorate.

Dicentrine, $C_{20}H_{21}O_4N$, crystallises from ether, alcohol, or ethyl acetate in prisms, m.p. 168°–169°, $[\alpha]_D + 62·1°$ in chloroform, and yields well-crystallised salts. The methiodide, $B.CH_3I.H_2O$ m.p. 224°, crystallises from dilute alcohol. The alkaloid contains two methoxyl groups.[5] Gadamer has suggested the following constitution for dicentrine, because of its similarity to glaucine (p. 243) :
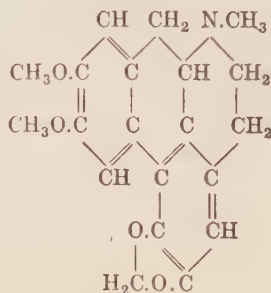
Dicentrine (Gadamer)

[1] Fischer and Soell, *Arch. Pharm.* 1902, **5**, 121.
[2] Heyl, *Arch. Pharm.* 1903, **241**, 313.
[3] *Ibid.* 1909, **247**, 201.
[4] Gadamer, *Apoth. Zeit.* 1901, **16**, 621 ; Danckwortt, *Arch. Pharm.* 1912, **250**, 590 ; 1922, **260**, 94.
[5] *Arch. Pharm.* 1911, **249**, 680.

According to Iwakawa [1] dicentrine in small doses produces narcosis, whilst in large doses it stimulates the medullary centres and causes convulsions, weakens the heart, and paralyses the respiratory centre.

ALKALOIDS OF *CHELIDONIUM MAJUS*

From the roots of this plant the following alkaloids have been isolated : chelerythrine, chelidonine, α- β- and γ-homochelidonines, protopine (p. 302), sanguinarine, and berberine (p. 208).[2]

Preparation. Schmidt and Selle extracted the dry powdered roots with alcohol acidified with acetic acid, and distilled off the alcohol after adding water. The resinous precipitate was filtered off, the filtrate made alkaline with ammonia and shaken out with chloroform. The residue left on distilling off this solvent was treated with cold dilute alcoholic hydrochloric acid, which left protopine and chelidonine hydrochlorides undissolved. Excess of ammonia solution was added to the filtrate when chelerythrine and α-homochelidonine were precipitated leaving β-homochelidonine in solution, from which it may be extracted by chloroform.

Chelerythrine, $C_{21}H_{17}O_4N$, was first obtained by Probst [3] from the root of *Chelidonium majus*, and later by the same author from *Sanguinaria canadensis* and *Glaucium luteum (flavum)*.[4] Battandier subsequently obtained it from *Eschscholtzia californica* and *Bocconia frutescens*,[5] and Murrill and Schlotterbeck from *Bocconia cordata*.[6] It was probably first obtained in a pure state by König and Tietz.[7] The best source of the alkaloid is the root of *Sanguinaria canadensis*.

It crystallises from alcohol in colourless prismatic leaflets, m.p. 207°, containing one molecule of alcohol, is readily soluble in

[1] *Arch. Exp. Path. Pharm.* 1911, **64**, 369.

[2] Godefroy, *Journ. Pharm.* 1824, **10**, 635 ; Probst. *Annalen*, 1839, **29**, 123 ; Will, *ibid.* 1840, **35**, 113 ; Eykman, *Rec. Trav. Chim.* 1884, **3**, 182 ; Schmidt and Selle, *Arch. Pharm.* 1890, **228**, 96, 441 ; Wintgen, *ibid.* 1901, **239**, 443 ; Schmidt, *ibid.* 1901, **239**, 395 ; and Schlotterbeck, *Amer. Journ. Pharm.* 1902, **74**, 584.

[3] *Annalen*, 1839, **29**, 120. *Cf.* Wintgen, *Arch. Pharm.* 1901, **239**, 448.

[4] *Annalen*, 1839, **31**, 250. *Cf.* Fischer, *Arch. Pharm.* 1901, **239**, 410, 429.

[5] *Bull. Soc. Chim.* 1896 [iii], **15**, 541. *Cf.* Fischer, *Arch. Pharm.* 1901, **239**, 421 ; and Brindejonc, *Bull. Soc. Chim.* 1911 [iv], **9**, 97.

[6] *Pharm. Journ.* 1900 [iv] **11**, 34.

[7] *Arch. Pharm.* 1893, **231**, 145, 161. *Cf.* Bauer and Hedinger, *ibid.* 1920, **258**, 167.

chloroform, sparingly so in alcohol or ether. The alkaloid absorbs carbon dioxide from the air, becoming yellow. The solutions fluoresce blue when the alkaloid is contaminated with its oxidation product, which is formed by mere exposure of solutions to air. The salts are intensely yellow. The hydrochloride, $B.HCl.H_2O$, forms citron-yellow needles, and the sulphate, $B.H_2SO_4.2H_2O$, golden yellow needles, sparingly soluble in water ; the platini-chloride, $B_2.H_2PtCl_6$, golden-yellow needles and the aurichloride $B.HAuCl_4$, long, silky, brown needles, m.p. 233° (*decomp.*). Sulphuric acid dissolves chelerythrine with the formation of a greenish solution, which slowly becomes dirty yellow. Sulphovanadic acid gives a violet-red tint changing to dark red. Chelerythrine has recently been re-examined by Karrer,[1] who finds that it contains a carbonyl group (phenylhydrazone, m.p. 158°), and that derivatives involving this group are no longer basic. On reduction with zinc and hydrochloric acid dihydrochelerythrine, m.p. 143°–144° (given later as 162°–163°), colourless and non-basic, is produced. With Grignard reagents, α-alkyldihydrochelerythrines are formed analogous to the alkyldihydroberberines (p. 214). According to Gadamer [2] chelerythrine does not contain a —CO group and the reactions which appear to indicate this occur in the same way as with cotarnine (p. 283) and berberine (p. 214). Two of the oxgyen atoms are shown to be present as a dioxymethylene group, and the other two as methoxy groups.[3] On these grounds Gadamer regards chelery-thrine as a quaternary base, which on liberation from its salts, immediately passes into the carbinol form (*cf.* berberine, p. 215). For relation to α homochelidonine, *see* p. 249.

Chelidonine, $C_{20}H_{19}O_5N.H_2O$, also occurs in *Stylophorum diphyllum*.[4] It is freed from protopine with which it occurs in the first separation (*see* p. 247) by regenerating the two alkaloids from the hydrochlorides by ammonia solution and digesting with ether, in which chelidonine is much less soluble and is purified by solution in a little dilute sulphuric acid and precipitation with strong hydrochloric acid as the hydrochloride. From this it is regenerated and crystallised from acetic acid. Chelidonine crystallises in monoclinic

[1] *Berichte*, 1917, **50**, 212 ; 1921, **54**, 2021 ; *Helv. Chim. Acta.* 1923, **6**, 232.

[2] *Arch. Pharm.* 1920, **258**, 148.

[3] Bauer and Hedinger ascribe the methyl iodide produced by the action of hydriodic acid on the alkaloid to the presence of an .NMe$_2$ group.

[4] Selle, *Arch. Pharm.* 1890, **228**, 96 ; Schlotterbeck and Watkins, *Pharm. Rev.* 1901, **19**, 453 ; *Pharm. Arch.* 1903, **6**, 141.

tablets, m.p. 135°–136°, $[\alpha]_D + 115°$ 24′ (in alcohol), is readily soluble in alcohol or ether, but insoluble in water : the hydrochloride B . HCl, and the nitrate, B . HNO₃, are crystalline and sparingly soluble in water.

It behaves as a tertiary base and contains a : NCH₃ group ; the oxygen atoms are present in the form of one hydroxyl group (acetyl derivative, m.p. 161°), and two dioxymethylene groups.

The alkaloid gives a deep crimson colour with strong sulphuric acid and tincture of guaiacum.

These data have been confirmed by Gadamer, who also finds that on oxidation with mercuric acetate chelidonine loses two atoms of hydrogen giving an intensely coloured salt of a dehydro-quaternary base, which very readily passes into a colourless carbinol base. On acetylation at a low temperature an O-acetylchelidonine (m.p. 185°) is produced, whilst at the boiling point of acetic anhydride a N-acetyl (m.p. 161°) derivative is formed with loss of a molecule of water and disappearance of optical activity probably due to the opening of a ring. When chelidonine methochloride is boiled with sodium hydroxide solution a strongly lævorotatory methine base is formed with a small amount of an optically inactive methine base. The O-acetyl derivative on oxidation with mercuric acetate yields a colourless, non-basic substance, which, especially in acid solution, gradually acquires a reddish-yellow colour and basic properties, and passes into dihydrochelerythrine, m.p. 160°–162° (p. 248). It is not, however, suggested that chelerythrine is directly related to chelidonine, though it is probably closely allied to α-homochelidonine [1] (see formula p. 250).

α-Homochelidonine, C₂₁H₂₃O₅N, has only been found in *Chelidonium majus*. It can be separated from the chelerythrine, with which it occurs (see p. 247), by digestion with ether, in which the latter is more soluble.

The alkaloid crystallises from acetic ether in prisms, m.p. 182°, is dextrorotatory, dissolves readily in chloroform or alcohol, but with difficulty in ether ; the aurichloride, B . HAuCl₄, forms reddish-yellow needles, but the hydrochloride, platinichloride, and other salts are amorphous. It contains two methoxyl groups, one hydroxyl group, one dioxymethylene group, and a CH₃N : group. According to Gadamer,[2] it behaves so similarly to chelidonine, that

[1] Gadamer, *Arch. Pharm.* 1919, **257**, 298 ; 1920, **258**, 148 ; 1921, **259**, 135.
[2] *Loc. cit.*

it can be regarded as chelidonine in which one of the dioxymethylene groups has been replaced by two methoxyl groups, and he assigns the following formulæ to the two alkaloids :
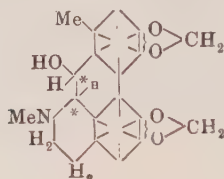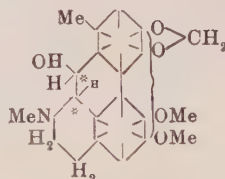
Chelidonine   α-Homochelidonine

and on this basis discusses the changes mentioned under chelidonine.

β-**Homochelidonine,** $C_{21}H_{23}O_5N$, (α-*allo-Cryptopine*) occurs also in *Sanguinaria canadensis*,[1] *Eschscholtzia californica*,[2] *Adlumia cirrhosa*,[3] and *Bocconia cordata*.[4] It crystallises from acetic ether in monoclinic prisms, m.p. 159°–160°, and is readily soluble in chloroform or acetic ether, less so in alcohol or ether. The hydrochloride, $B.HCl.1\frac{1}{2}H_2O$, forms colourless needles, and is readily soluble in water ; the nitrate, hydrobromide and hydriodide are also crystalline ; the platinichloride, $B_2.H_2PtCl_6.2\frac{1}{2}H_2O$, is amorphous, but the aurichloride, $B.HAuCl_4$, m.p. 187°, forms blood-red crystals. It is a tertiary base and yields two methiodides, m.p. 185° and m.p. 211°. The alkaloid dissolves in sulphuric acid, forming a yellow solution changing to carmine-red. β-Homochelidonine contains two methoxyl groups. According to Schmidt, β- and γ-homochelidonines (*see below*) are physical isomerides and dihydro derivatives of α-homochelidonine (p. 249), but the latter view is no longer tenable. Fischer[5] states that β- and γ-homochelidonines are interconvertible and yield the same aurichloride.[6]

γ-**Homochelidonine,** $C_{21}H_{23}O_5N$ (β-*allo-Cryptopine*). The principal source of this alkaloid is *Sanguinaria canadensis*,[7] but it also occurs in *Zanthoxylum brachyacanthum* (p. 222), and to a small extent in the root of *Chelidonium majus*.[6] The alkaloid is a physical isomeride

[1] König and Tietz, *Arch. Pharm.* 1893, **231**, 145.

[2] Fischer, *ibid.* 1901, **239**, 409.

[3] Schlotterbeck and Watkins, *Pharm. Arch.* 1903, **6**, 17.

[4] Hopfgärtner, *Monats.* 1898, **19**, 179 ; Murrill and Schlotterbeck, *Pharm. Journ.* 1900 [iv], **11**, 34 ; Schlotterbeck and Blome, *Pharm. Rev.* 1905, **23**, 310 ; Momoya, *J. Pharm. Soc. Japan*, 1919, No. 444 (*Chem. Soc. Abstr.* 1919 [i], 450).

[5] *Arch. Pharm.* 1901, **239**, 409.

[6] *Cf.* Wintgen, *ibid.* 1901, **239**, 438 ; and Gadamer, *ibid.* 1920, **258**, 156.

[7] König and Tietz, *ibid.* 1893, **231**, 145.

of β-homochelidonine, and separates with the latter, in large colourless tablets, m.p. 169° (*dry*), from acetic ether, which can be mechanically separated from the small prisms of the associated isomeride. It is best prepared by extracting blood-root, *Sanguinaria canadensis*, with alcohol containing acetic acid, concentrating the extract and pouring it into water. The filtrate from this is made alkaline with ammonia solution. The precipitate contains sanguinarine, chelerythrine and protopine, whilst β- and γ-homochelidonines remain in the filtrate and may be extracted together with a little protopine by concentrating the filtrate, adding more ammonia and shaking out with chloroform.

It crystallises with $\frac{1}{2}$ mol. of alcohol in stout colourless needles, m.p. 170°–171° (*dry*), $[\alpha]_D = 0°$. The hydrochloride, $B.HCl.1\frac{1}{2}H_2O$, forms small colourless needles, m.p. 175° (*decomp.*), and the aurichloride, $B.HAuCl_4$, blood-red warty crystals, m.p. 192° (*decomp.*), the latter is said to be identical with β-homochelidonine aurichloride.[1] The methiodide, $B.CH_3I.2\frac{1}{2}H_2O$, forms bright yellow prisms ; the alkaloid is a tertiary base and contains two methoxyl groups, a dioxymethylene group and one $: NCH_3$ group.[2]

Constitution of β- and γ-Homochelidonines. Gadamer [3] has now shown that these two alkaloids are not homologues of chelidonine, and suggests they should be renamed α- and β-allocryptopines as they are closely related to and isomeric with cryptopine (*see* p. 298).

Gadamer's work relates solely to β-homochelidonine, but as he regards γ-homochelidonine as a physical isomeride of this the same structural formula is assigned to both.

When warmed with phosphoryl chloride β-homochelidonine passes into the chloride of a quaternary base which is identical with dihydroanhydroberberine methochloride, $C_{20}H_{19}O_4N.CH_3Cl$, colourless needles, m.p. 200°–201°, a reaction completely analogous with the conversion of cryptopine into *iso*cryptopine chloride (p. 301). Similarly β-homochelidonine on reduction by sodium amalgam and dilute sulphuric acid forms a dihydro-base, m.p. 167°–168°, which with phosphoryl chloride yields tetrahydroanhydroberberine methochloride, $C_{21}H_{24}O_4NCl.3H_2O$, m.p. 249°–251° (*cf.* p. 223).

These changes Gadamer explains by the following formula for

[1] Fischer, *Arch. Pharm.* 1901, **239**, 409.
[2] Jowett and Pyman, *Trans. Chem. Soc.* 1913, **103**, 299.
[3] *Arch. Pharm.* 1919, **257**, 298 ; **1920**, **258**, 148.

β-homochelidonine to which for comparison the formula for crypto-dine is added :

β-Homochelidonine   *Cryptopine*   *Berberine* (ammonium form)
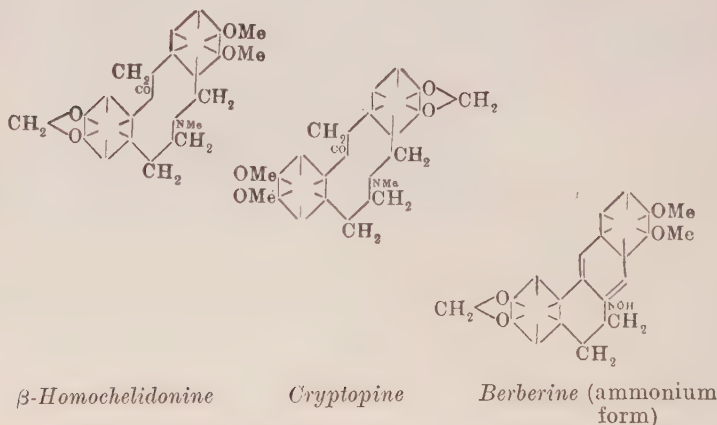
The conversion of β-homochelidonine into the berberine deriva-tives referred to above, merely involves changes in the reduced pyridine ring of the type already discussed (p. 219) thus :

β-*Homochelidonine*   *Dihydroanhydroberberine methochloride*

Dihydro-β-homochelidonine   *Tetrahydroanhydroberberine methochloride*
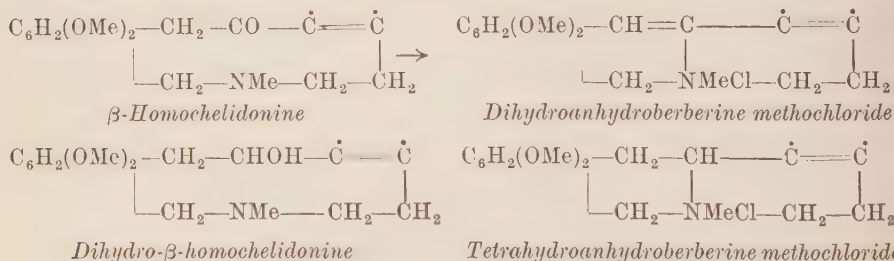
Sanguinarine, $C_{20}H_{15}O_4N.1H_2O$ or $1C_2H_5OH$, the principal alkaloid of *Sanguinaria canadensis* (blood-root), was obtained from this source by Dana,[1] and has since been found in *Bocconia cordata*, *Chelidonium majus*, and *Stylophorum diphyllum* (see p. 311).

The separation of sanguinarine from the chelerythrine and protopine with which it is precipitated (p. 247) is difficult, and for details the original papers should be consulted.[2]

Sanguinarine crystallises from acetic ether or alcohol in *colourless* groups of needles, m.p. 212° (from alcohol), and dissolves in the usual organic solvents, forming solutions that are fluorescent.   It

[1] *Mag. Pharm.* 1829, **23**, 125.
[2] *Arch. Pharm.* 1893, **231**, 145, 161 ; 1901, **239**, 409.   *Bull. Acad. Sci. Crac.* 1910, p. 235.

slowly reddens in air, due to the formation of the carbonate. The salts are *deep red* in colour ; the hydrochloride, $B.HCl.5H_2O$, and the nitrate, $B.HNO_3.H_2O$, form red needles, but the gold and platinum salts are amorphous. The base contains one methoxyl group. With sulphovanadic acid a dark red solution passing into violet is obtained.

PHYSIOLOGICAL ACTION OF CHELIDONIUM ALKALOIDS. *Chelerythrine* is poisonous. It paralyses the central nervous system without any initial increase in irritability, resembles protopine in its muscular action, and, like sanguinarine, first irritates and then paralyses the sensory nerve terminations.

Chelidonine and *α-homochelidonine* resemble morphine in their effects on the central nervous system, but are only slightly toxic. According to Hanzlik [1] the former resembles papaverine rather than morphine in its action, and could be substituted for it for use in medicine especially as an antispasmodic.

β-Homochelidonine closely resembles protopine and cryptopine in action.

Sanguinarine causes tetanus and excitement, and, therefore, occupies a place between codeine and thebaine in the opium group of alkaloids. It resembles protopine in its action on muscle, and at first irritates and then paralyses the sensory nerve endings in the skin, when applied locally.

None of these alkaliids is used as such in medicine, but the latex of *Chelidonium majus* and extracts of the plant were formerly employed, and a tincture of *Sanguinaria canadensis* root is official in the United States Pharmacopœia. Sanguinaria preparations appear to be used principally as expectorants and emetics.

ALKALOIDS OF OPIUM

Opium is the sun-dried latex of the unripe fruit of the opium poppy *Papaver somniferum*, which has been cultivated from very early times for the sake of this drug. It is produced in many tropical and sub-tropical countries, but only on a large scale in India, China, Persia, South-eastern Europe and Asia Minor. That used in medicine is mostly the Asia Minor variety (Turkey and Smyrna opium), but a good deal of Persian and Indian opium is imported for the manufacture of the opium alkaloids.

The large scale on which the two principal alkaloids of opium, morphine and codeine are manufactured, has made it possible to

[1] *Journ. Amer. Med. Assoc.* 1920, **75**, 1324.

conduct investigations on practically unlimited supplies of this drug, with the result that many alkaloids have been isolated from it. At present twenty-five opium bases are known ; their names and formulæ are as follows :

Morphine	.	$C_{17}H_{19}O_3N$	Laudanidine .	$C_{20}H_{25}O_4N$
Codeine .	.	$C_{18}H_{21}O_3N$	Codamine .	$C_{20}H_{25}O_4N$
Neopine .	.	$C_{18}H_{21}O_4N$ or	Pseudopapaverine	$C_{21}H_{21}O_4N$
		$C_{18}H_{21}O_3N$	Papaveramine .	$C_{21}H_{25}O_6N$
Pseudomorphine		$(C_{17}H_{18}O_3N)_2$	Xanthaline [1] .	$C_{20}H_{19}O_5N$
Thebaine .	.	$C_{19}H_{21}O_3N$	(Papaveraldine)	
Narcotine	.	$C_{22}H_{23}O_7N$	Protopapaverine	$C_{19}H_{19}O_4N$
Gnoscopine	.	$C_{22}H_{23}O_7N$	Meconidine .	$C_{21}H_{23}O_4N$
(dl-narcotine)			Lanthopine .	$C_{23}H_{25}O_4N$
Oxynarcotine .		$C_{22}H_{23}O_8N$	Protopine .	$C_{20}H_{19}O_5N$
Narceine .	.	$C_{23}H_{27}O_8N$	Cryptopine .	$C_{21}H_{23}O_5N$
Papaverine	.	$C_{20}H_{21}O_4N$	Tritopine .	$(C_{21}H_{27}O_3N)_2O$
Laudanosine	.	$C_{21}H_{27}O_4N$	Rheadine .	$C_{21}H_{21}O_6N$
Laudanine	.	$C_{20}H_{25}O_4N$	Hydrocotarnine [1]	$C_{12}H_{15}O_3N$

Numerous analyses of opium from different sources have been recorded, and, as a considerable amount of attention has been directed to the estimation of morphine, widely different methods have been employed, so that it is difficult to collect analytical results which are strictly comparable ; but as far as possible, this has been done in compiling the table on p. 255, showing the morphine and narcotine values of different kinds of opium.[2]

These figures, though comparable, are misleading, as opium from the Balkans and Smyrna frequently contains up to 15 per cent. of morphine. Further, they confirm the impression conveyed by many authors that Indian opium is always low in morphine. The latter is due to the fact that up to 1914 most Indian opium was prepared for smoking, and for this purpose little attention need be paid to the amount of morphine present. Since 1914 special efforts have been made to prepare in India opium suitable for medicinal purposes,[3]

[1] These are possibly decomposition products of papaverine and narcotine.

[2] Flückiger, *Pharm. Journ.* 1875 [iii], **5**, 845 ; and Dott, *Year Book of Pharmacy*, 1876, 498.

[3] For information on this point *see* papers by Annett and collaborators, *Agricultural Journal of India*, 1920, **15**, 124 ; 1921, **16**, 19 ; *Biochemical Journal*, 1920, **14**, 618 ; 1922, **16**, 765 ; *Memoirs of the Dept. of Agriculture, India*, 1921, **6**, No. 1 ; 1922, **6**, No. 6 ; *Bulletin No.* 116. *Agricultural Inst. Pusa*, 1921.

PLATE IV.
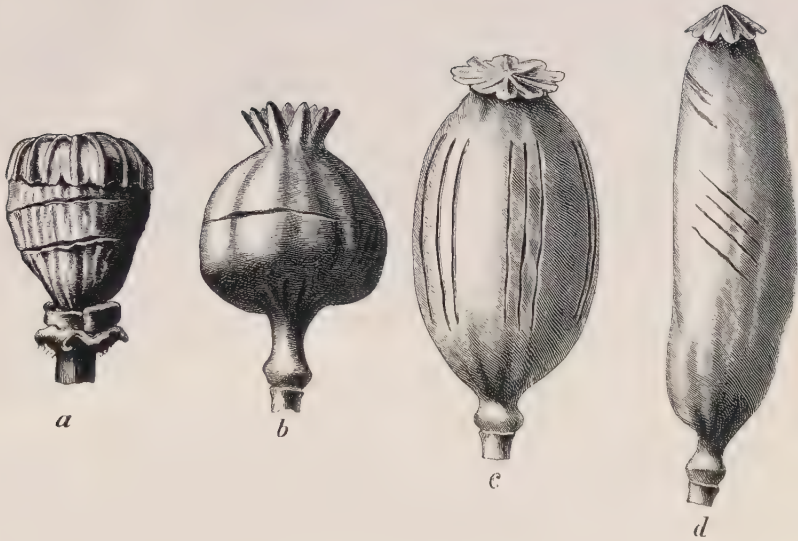
Fig. 1.—Opium. Poppy capsules, showing the different methods of incising. (Vogl, from specimens in the Museum of the Pharmacological Institute, Vienna.)
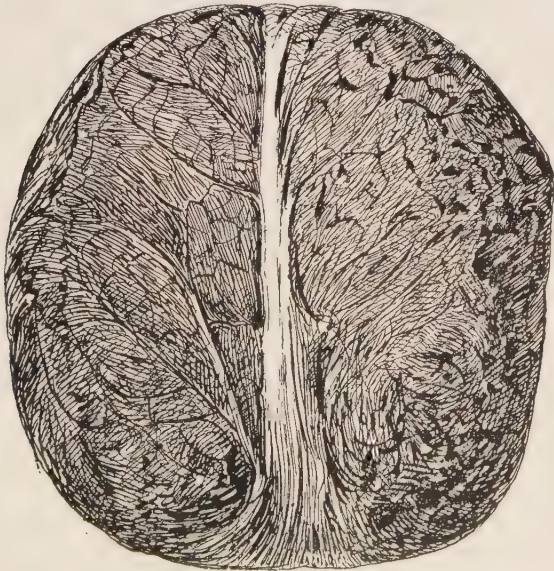
Fig. 2.—Turkey Opium. Slightly reduced. (*Pharmaceutical Journal.*)

Percentages of Morphine and Narcotine in Opium

Source of Opium			Morphine (average)	Narcotine (average)	Author
Indian—					
Patna	.	.	8·6 [1]	4·0	Flückiger.
Malwa	.	.	6·50 6·1 [1]	— 4·7	Dott. Flückiger.
Jeypore	.	.	4·6 to 7·75 [1]	4·5 to 7·1	Dunstan and Brown.
Sind	.	.	3·8 [1]	3·1	Flückiger.
Hyderabad .	.	.	3·2 [1]	5·4	Flückiger.
Smyrna .	.	.	10·0 [2]	—	Dott.
Egyptian	.	.	7·0 5·8 [1]	— 8·7	Dott. Flückiger.
Persian	.	.	7·1 [1] 7·2 [3]	6·4 —	Flückiger. Dott.
Chinese	.	.	4·3 to 11·2	1·9 to 6·6	F. Browne.

[1] These figures represent pure morphine, determined by Flückiger's method, and are probably below the truth.

[2] Average of twelve samples ranging from 6·9 to 12·3 per cent. of hydrated morphine.

[3] Mean of two samples containing 6·00 and 8·50 per cent. of hydrated morphine.

and the morphine value of the Indian drug has risen steadily since that date. Indian opium has the further advantage of being richer in codeine than that produced elsewhere. Investigations conducted at the Imperial Institute [4] show that the amount of morphine in Indian opium varies from 9·5 to 14·2 per cent., codeine 1·8 to 4·0, and narcotine 3·9 to 7·6, so that there seems to be no reason why opium equal in quality to the " Turkey " or " Smyrna " drug should not be obtainable from India.

Estimation of Alkaloids in Opium

MORPHINE. The poisonous character of this base, the most important constituent of opium, lends particular interest to the problem of accurately determining the amount of it contained in the crude drug and its medicinal preparations, and many processes have been devised for this purpose.

The British Pharmacopœia (1914) adopts the following method : 8 grm. of opium dried at 60° and in No. 50 powder are mixed with 2 grm. of slaked lime, and stirred in a mortar with 20 c.c. of water. The mixture is then diluted with 60 c.c. of water and occasionally stirred during half an hour. To 51 c.c. of the filtrate (5 grm. of opium), 5 c.c. of alcohol (90 per cent.) and 25 c.c. of ether are

[4] *Bulletin of the Imperial Institute,* 1915, **13**, 207 ; 1919, **17**, 1.

added, and the mixture well shaken. To precipitate the morphine from its solution in the lime water, 2 grm. of ammonium chloride are added, the mixture well shaken during thirty minutes and set aside for twelve hours by which time the morphine will have crystallised out. The ethereal layer is collected in a pipette and filtered through two small counterbalanced filter papers placed one within the other and previously wetted with ether ; 10 c.c. of ether are added to the contents of the vessel, the mixture shaken and the ether again transferred by a pipette, the filter papers being washed with small portions of ether, using 5 c.c. in all, and allowed to dry in the air. The crystals which remain in the vessel are filtered off through the two filter papers and washed with a saturated solution of morphine in chloroform water. The crystals of morphine are dried first at 60° and finally at 115° for two hours and weighed, the second filter being used to counterbalance the first.

The purity of the morphine is checked by dissolving 0·2 grm. of the dry crystals in 10 c.c. of $N/10$ sulphuric acid and titrating back with $N/10$ sodium hydroxide, using methyl orange as indicator. One cubic centimetre of the acid is equal to 0·0285 grm. of morphine. The weight of pure morphine indicated by the titration as present in the crystals, plus 0·051 grm., representing the average loss by this method of estimation, should amount to not less than 0·45 and not more than 0·55 grm., corresponding to about 10 per cent. of morphine in the dry powdered opium. A similar process is used for the official galenical preparation of the drug.[1]

The United States Pharmacopœia (9th Rev.) prescribes the following process for opium : 8 grm. of opium, in small pieces if moist, or in fine powder if dry, are mixed with 80 c.c. of water in a 250 c.c. flask and shaken at least every ten minutes during three hours, and the mixture then poured on a moistened 12 cm. filter. The residue on the filter is washed with enough water to increase the filtrate to 120 c.c., then mixed in a mortar to a smooth paste and transferred with the help of 50 c.c. of water to the flask and shaken well. The mixture is again transferred to the filter and the residue washed with 75 c.c. of water. The mixed filtrates and washings are then evaporated on the water bath to 40 grm. This is next transferred to a 50 c.c. graduated flask, using enough water for washing to make the volume of extract 50 c.c. Four grammes of slaked lime are then placed in a mortar with 10 c.c. of the extract

[1] *Cf.* Annett and Singh, *Analyst*, 1918, **43,** 205 ; Dott, *Pharm. Journ.* 1918, **101,** 318.

and rubbed into a smooth paste ; the rest of the extract is gradually added, 10 c.c. of water being used to wash out the flask, and the whole stirred for fifteen minutes. The mixture is filtered through a 10 cm. filter and 30 c.c. of the filtrate (= 4 grm. of opium) placed in an Erlenmeyer flask with 2 c.c. of alcohol, 15 c.c. of ether, and 1 grm. of ammonium chloride, the mixture shaken frequently during one hour and set aside for twelve hours, after which the precipitated morphine is washed (by decantation) with morphinated water, the ethereal layer, 15 c.c. more ether used to wash the liquor and crystals in the flask, the mother liquor and washings being all run through a small plug of cotton wool in a funnel to prevent any loss of morphine. The cotton wool is returned to the flask containing the washed crystals, and 20 c.c. of $N/10$ sulphuric acid passed through the funnel into the flask followed by ten c.c. of water to wash the funnel. When solution is complete the excess of acid is titrated by means of $N/50$ potassium hydroxide solution, using cochineal as indicator. Each cubic centimetre of $N/10$ sulphuric acid used corresponds to 0·0285 grm. of anhydrous morphine.[1]

For the estimation of morphine in solutions containing this alkaloid alone, warm amyl alcohol is a useful extracting medium or a mixture of cresol, 2 parts, with amyl alcohol, 1 part.[2]

OTHER ALKALOIDS. It is not often necessary to estimate other alkaloidal constituents of opium than morphine, but occasionally determinations of narcotine or codeine are required. Narcotine may be estimated by extracting dried opium with dry ether or benzene, and shaking the solution with ammonia, which removes narceine. The narcotine left on distilling off the solvent is dried and weighed.[3]

For codeine, methods have been published by van der Wielen,[4] Caspari,[5] Andrews [6] and Annett, and co-workers.[7]

[1] For other methods *see* Schidrowitz, *Analyst*, 1904, **29**, 144 ; Prescott and Gordin, *J. Amer. Chem. Soc.* 1898, **20**, 724 ; Asher, *Amer. J. Pharm.* 1906, **78**, 262 ; Léger, *J. Pharm. Chim.* 1903 [ii], **17**, 553 ; van der Wielen, *Bull. Sci. Pharm.* 1910, **17**, 59 ; Thorburn, *J. Ind. Eng. Chem.* 1911, **3**, 754 ; Dohme, *Chem. Soc. Abstr.* 1915 [ii] 711 ; Rakshit, *Journ. Soc. Chem. Ind.* 1917, **36**, 989 ; Heiduschka and Faul, *Arch. Pharm.* 1917, **255**, 172 ; Tingle, *Amer. J. Pharm.* 1918, **90**, 689, 788, 851 ; Jermstad, *Ber. Deut. Pharm. Ges.* 1920, **30**, 392 ; Nicholls *Analyst*, 1923 [ii], 196.

[2] Tickle, *Pharm. Journ.* 1907 [iv], **24**, 162.

[3] For a more accurate method *see* Annett and Bose, *Analyst*, 1923, **48**, 53.

[4] *Pharm. Zeit.* 1903, **48**, 267.

[5] *Apoth. Zeit.* 1904, **19**, 874.

[6] *Analyst*, 1911, **36**, 489.

[7] *Ibid.* 1920, **45**, 321 ; 1922, **47**, 16. For special methods for these

General methods for the separation and estimation of the chief opium alkaloids have been described by Plugge [1] and by Dott.[2]

Isolation of Opium Alkaloids. Hesse has given the following scheme for the separation of the rarer opium bases contained in the mother liquors (*see* p. 259) produced in the manufacture of morphine and codeine.[3] The opium is extracted with water and calcium chloride added to the aqueous extract to precipitate calcium meconate. The filtrate on gradual concentration deposits hydrochlorides of morphine, pseudomorphine and codeine in this order. The mother liquor is mixed with an equal bulk of water and excess of ammonia ; the precipitate thus obtained is dissolved in acetic acid, filtered, purified by shaking with ether, and then made alkaline with caustic soda, which (1) precipitates papaverine, narcotine, thebaine, some cryptopine, protopine, laudanosine and hydrocotarnine ; (2) dissolves lanthopine, laudanine, codamine, some cryptopine and meconidine, if the latter is present. The precipitated alkaloids are dissolved in dilute alcohol as far as possible, the liquid slightly acidified with acetic acid and three times its volume of boiling water added, which precipitates *papaverine* and *narcotine*. The filtrate from these is evaporated to remove alcohol, and tartaric acid added to precipitate *thebaine hydrogen tartrate*. The mother liquor is neutralised with ammonia, mixed with 3 per cent. by weight of sodium bicarbonate, and set aside for a week, filtered, and ammonia added. The precipitate thus obtained is extracted with boiling benzene, which removes *laudanosine* and *hydrocotarnine*. By shaking the benzene solution with aqueous sodium bicarbonate, *laudanosine* is precipitated, and by passing through it hydrogen chloride, *hydrocotarnine chloride* is obtained. The bases insoluble in benzene are protopine and cryptopine, which may be separated by conversion into the hydrochlorides, and washing with a very little water, the *cryptopine* salt being very soluble, and the *protopine* salt only slightly so in water.

The alkaloids which remained dissolved in the caustic soda solution are obtained by neutralising with dilute hydrochloric acid, adding ammonia, extracting with ether, and shaking out the ethereal

and other opium alkaloids *see* among recent papers, Gsell and Marschalkó, *Zeit. Anal. Chem.* 1914, **53**, 673 ; Anneler, *Arch. Pharm.* 1920, **258**, 130 ; (meconic acid) Annett and Bose, *Analyst*, 1922, **47**, 387.

[1] *Rec. Trav. Chim.* 1887, **6**, 157. *Cf.* Annett and Bose, *Analyst*, 1923, **48**, 53.

[2] *Allen's Organic Analysis*, 4th ed. vol. vi, **p. 372**.

[3] *Cf.* Kauder, *Arch. Pharm.* 1890, **228**, 419.

solution with acetic acid ; *lanthopine* separates in the course of twenty-four hours, when the acid liquid is neutralised with ammonia. On adding excess of ammonia to the filtrate, laudanine, codamine and cryptopine, are precipitated. This precipitate is dissolved in a little boiling dilute alcohol, which on cooling deposits *laudanine* and *cryptopine*, and from the mother liquor *codamine* may be obtained by evaporation and addition of ether. Hesse's scheme does not provide for the separation of narceine and meconidine, and he assumes that the second of these two alkaloids is decomposed during extraction by this method.

MORPHINE, CODEINE, THEBAINE

Morphine, $C_{17}H_{19}O_3N$. Already in the seventeenth and eighteenth centuries attempts had been made to prepare from opium the " principle " to which it owes its physiological activity and the extracts obtained in the course of these experiments were employed in medicine under the name of *Magisterium Opii*. Early in the nineteenth century Bucholz endeavoured to crystallise from aqueous extracts of the drug a " salt " which could be used in place of opium ; and about the same time Derosne, an apothecary practising in Paris, observed the separation of a crystalline substance, when a syrupy aqueous extract of opium was diluted with water. This crystalline material was probably narcotine, or a mixture of that alkaloid with morphine. Seguin in 1804, read to the Institute of France a paper entitled " *Sur l'opium*," in which he described the isolation of morphine, although he did not recognise its basic character. This paper was not published till 1814, and, in the meantime, Sertürner had obtained both morphine and meconic acid from opium, and pointed out that the former was the first member of a new class of substances, " the vegetable alkalis." [1] The composition of the alkaloid was first determined by Liebig in 1831, who represented it by the formula, $C_{34}H_{36}O_6N_2$, which was reduced by Laurent in 1847 to the simpler formula, $C_{17}H_{19}O_3N$, now in use.

Preparation. Morphine can be prepared by the following process. The opium is extracted with warm water, the extract mixed with chalk, and evaporated to a small volume. Calcium chloride is then added and the liquid diluted with water. The precipitate of resin, calcium meconate, etc., is filtered off, and the filtrate evaporated to a low bulk, when a mixture of morphine and codeine hydro-

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[1] *Gilbert's Annalen*, 1817, **55**, 61.

chlorides crystallises out. This mixture is pressed, redissolved in water, and excess of ammonia added, which precipitates the morphine and a little codeine. The morphine may be freed from traces of codeine [1] by washing with ether or benzene, or it may be purified by recrystallising from hot water and then regenerating the alkaloid and recrystallising from hot alcohol. The codeine may be recovered from the mother liquor referred to above by adding potash solution, or the mother liquor may be evaporated to a low bulk, when codeine crystallises out.[2]

Properties. Morphine crystallises from alcohol in colourless, trimetric prisms containing $1H_2O$, becomes anhydrous at $100°$, and then melts with decomposition at $254°$. It is bitter to the taste and sparingly soluble in most solvents. The solubilities given by different observers vary greatly (*e.g.*, boiling alcohol 1 in 30 to 1 in 36, in cold alcohol 1 in 210 to 1 in 300), and Prescott has pointed out that the physical condition of the alkaloid used affects the solubility to a considerable extent : thus he states that morphine in powder is nearly three times as soluble in ether as the crystalline alkaloid.[3] Müller [4] gives the following figures : water (1 in 3,533), ether (1 in 7,632), benzene (1 in 1,599), chloroform (1 in 1,525), ethyl acetate (1 in 537). According to Florio the solubility in amyl alcohol is about 1 in 50 at $78°$. Müller's figure for solubility in benzene is unusually high, and though Prescott [3] states that freshly precipitated morphine dissolves in 1,997 parts of benzene whilst the crystallised alkaloid dissolves in 8,930 parts, the alkaloid is generally stated to be insoluble in benzene. Morphine is readily soluble in limewater (1 in 100 at $25°$), or in alkali hydroxide solutions, but less so in ammonia solution (1 in 117, sp. gr. $0·97$, Duplos). The base is lævorotatory, $[\alpha]_D^{23} - 130·9°$ in methyl alcohol, $- 70°$ in excess of alkali. It is a monoacidic base, and its salts, which are usually well-crystallised, are neutral to litmus and methyl orange. Those chiefly used in medicine are the sulphate, hydrochloride, and acetate, though the tartrate, bimeconate, and others have also been employed. The sulphate, $B_2 . H_2SO_4 . 5H_2O$, forms small silky crystals or cubical masses from water, is soluble in water (1 in $15·3$ at $25°$, or 1 in $0·6$ at $80°$), or alcohol (1 in 465 at $25°$, or 1 in 187 at $60°$). It chars at $250°$, but does not melt. It is lævorotatory, $[\alpha]_D^{15} - 100·47° + 0·96c$ in

[1] Andrews, *Analyst*, 1911, **36**, 489.
[2] Gregory, *Annalen*, **7**, 263.
[3] *Journ. Amer. Chem. Soc.* 1907, **29**, 405.
[4] *Apoth. Zeit.* 1903, **18**, 257.

water. The hydrochloride, $B.HCl.3H_2O$, forms colourless silky needles from water, $[\alpha]_D^{15} - 100.67° + 1.14c$ in water (Hesse), or $- 111.5°$ at $25°$ in dry alcohol (Schryver and Lees), is soluble in water (1 in 17·2 at 25°, or 1 in 0·5 at 80°), or alcohol (1 in 42 at 25°, or 1 in 35·5 at 60°). The hydrobromide, $B.HBr.2H_2O$, and the hydriodide, $B.HI.2H_2O$, form long needles. The acetate, $B.CH_3COOH.3H_2O$, forms a crystalline colourless powder, m.p. 200° (*decomp.*), $[\alpha]_D - 77°$ in water, $- 100.4°$ in dry alcohol. It is very soluble in water (1 in 2·25 at 25°), less so in alcohol (1 in 21·6 at 25°), and sparingly so in chloroform (1 in 480 at 25°).

Detection. Morphine is at most coloured faintly pink by cold sulphuric acid, but becomes dirty green and then brown on warming. With nitric acid it gives an orange-red coloration. With sulphuric acid and potassium iodate it yields a brown coloration, and with sulphuric acid containing potassium dichromate, a green tint after a time, and with sulphuric acid containing selenious acid, blue changing to green and then brown. Morphine salts in solution, on warming with potassium ferricyanide solution containing a little neutral ferric chloride, give after a time a blue precipitate. A few drops of neutral ferric chloride solution added to a solution of a morphine salt produce a blue coloration which disappears on warming or on addition of an acid or alcohol.[1]

Apomorphine, $C_{17}H_{17}O_2N$. When morphine or its hydrochloride is heated in sealed tubes with strong hydrochloric acid at 140°, apomorphine hydrochloride is formed by the loss of a molecule of water from the parent alkaloid.[2] Apomorphine is separated from any unchanged morphine by adding excess of sodium bicarbonate to the mixture and extracting with ether or chloroform. From the latter it may be crystallised in the absence of oxygen or it may be isolated as the hydrochloride by shaking with a little hydrochloric acid.

Apomorphine forms colourless prisms from ether with 1 mol. of solvent, but is usually seen as an amorphous white substance which becomes green on exposure to air, a change which occurs even more readily in solution. Unlike morphine, it is readily soluble in chloroform or ether, and the alkaloid, which has become green by exposure to air, forms a bluish-red solution in ether, and gives a violet solution

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[1] For other methods described recently for the detection of morphine. *see* Herrmann, *Biochem. Zeits.* 1912, **39**, 216; Oliver, *Chem. Soc. Abstr.* 1915 [ii], 75; Grimbert and Leclere, *J. Pharm. Chim.* 1915 [vii], **11**, 23.

[2] Matthiessen and Wright, *Annalen*, 1870, *Suppl.* **7**, 170, 177.

in chloroform. The alkaloid is not coloured by sulphuric acid, gives a crimson tint with nitric acid and a rose-red changing to violet and black with ferric chloride. With mercuric chloride and sodium acetate, it produces a blue colour soluble in amyl alcohol. This reaction is said to be obtainable with 1 part in 500,000 of the alkaloid.[1] The hydrochloride, B.HCl, is the salt generally used in medicine ; it forms minute crystals, which become greenish in light and air. It is soluble in water (1 in 39·5 at 25°) or alcohol (1 in 38·2 at 25°), less so in ether (1 in 1,864 at 25°), and is neutral to litmus. The taste is slightly bitter. When a solution of 1 part in 10,000 of water is shaken with chloroform and then sodium hydroxide, the chloroform is coloured blue and the aqueous layer reddish-violet.

When 0·05 grm. of the hydrochloride is shaken with 0·5 per cent. ferrous sulphate solution, the latter becomes blue and then black, the blue colour being restored by alcohol. On methylation[2] apomorphine yields *apo-ψ-*CODEINE, $C_{18}H_{19}O_2N$, crystallising in brilliant plates, m.p. 110°–111°, $[\alpha]_D^{15} - 90°$ in alcohol, which is also produced when codeine or ψ-codeine is heated with oxalic acid.[3] It stands in the same relation to codeine as apomorphine to morphine (*see*, however, p. 264).

Pseudomorphine (*Oxydimorphine, dehydromorphine*), $C_{34}H_{36}O_6N_2$. $3H_2O$. This alkaloid was isolated from opium by Pelletier in 1835, and was subsequently obtained pure by Hesse.[4] The formation of a similar substance by the action of various mild oxidising agents on morphine was observed by Schützenberger and by Polstorff[5] among others. It occurs with morphine and codeine hydrochlorides separated from opium as described above (p. 258), and is isolated by precipitation of the morphine with ammonia in alcoholic solution ; on distilling the alcohol from the filtrate and replacing it by water, the addition of ammonia causes the separation of pseudomorphine, which is purified by crystallisation from hot ammonia solution. The alkaloid is best prepared by gentle oxidation of morphine by potassium permanganate in presence of sodium bicarbonate. It forms crusts or silky needles, is insoluble in water or organic solvents, but dissolves in warm aqueous or alcoholic ammonia, or in aqueous alkali hydroxide solutions. The hydrochloride, B.2HCl.2H_2O or $4H_2O$ or $6H_2O$, has $[\alpha]_D - 103·13°$ (anhydrous salt). Pseudo-

[1] Grimbert and Leclère, *Journ. Pharm. Chim.* 1915 [vii], **11**, 23.
[2] Knorr and Raabe, *Berichte*, 1908, **41**, 3050.
[3] Knorr and Roth, *ibid.* 1907, **40**, 3356.
[4] *Annalen*, 1867, **141**, 87 ; 1884, **222**, 234.
[5] *Berichte*, 1880, **13**, 86.

morphine mixed with sucrose dissolves in sulphuric acid, forming a dark green solution changing to brown. The alkaloid is tasteless and physiologically inactive.

Codeine, $C_{18}H_{21}O_3N$. This alkaloid was isolated from opium by Robiquet in 1832.[1] It occurs in opium to the extent of 0·1 to 3 per cent., and may be prepared therefrom by the process already described (p. 260). It is a methyl ether of morphine [2] and is usually made from the latter by methylation, for which there are numerous patents,[3] for example, by the action of potassium methyl sulphate on morphine dissolved in methyl alcohol in presence of potassium hydroxide, or by the action of dimethyl sulphate on alkali or alkaline earth derivatives of morphine. The solvent is distilled from the reaction mixture, water added, any unchanged morphine precipitated with ammonia and the codeine extracted with benzene.

Properties. Codeine crystallises with $1H_2O$ from water in large translucent orthorhombic prisms, m.p. 155° (*dry*), $[\alpha]_D - 137·7°$ in alcohol, or $- 111·5°$ in chloroform, and is generally seen in this form, but it separates from dry ether in small anhydrous prisms. Its taste is slightly bitter. Codeine is moderately soluble in water (1 in 120 at 25°, 1 in 59 at 80°), or ammonia solution (1 in 68 at 15·5°), more so in ether (1 in 12·5 at 25°), and readily so in alcohol (1 in 1·6 at 25°, 1 in 0·92 at 60°) or chloroform (1 in 0·66 at 25°). It differs from morphine in being fairly soluble in anisole (1 in 6·5 at 16°) or cold benzene (1 in 10·4), and in its sparing solubility in aqueous solutions of alkali hydroxides.

Codeine is a strong, monoacidic base, forming salts, which are neutral to litmus or methyl orange. The free base and also the sulphate and phosphate are used in medicine. The hydrochloride, $B.HCl.2H_2O$, forms short needles soluble in water (1 in 26 at 15°), $[\alpha]_D^{22·5} - 108·2°$ in water; the salt effloresces in air and loses its water completely and readily at 120°. The sulphate, $B_2.H_2SO_4.$ $5H_2O$, forms rhombic prisms, m.p. 278° (*decomp.*), $[\alpha]_D^{15} - 101·2°$ in water, which readily lose $2H_2O$ on exposure to air, and are completely dehydrated at 100°. It is soluble in water (1 in 30 at 25°), sparingly so in alcohol (1 in 1,035 at 25°), insoluble in ether. The phosphate, $B.H_3PO_4.1, 1\frac{1}{2}$ or $2H_2O$, forms needle-shaped crystals, m.p. 235° (*decomp.*), and is soluble in water (1 in 2·25 at 25°), less so in alcohol (1 in 261 at 25°).

[1] *Annalen*, 1832, **5,** 106.

[2] Grimaux, *compt. rend.* 1881, **92,** 1140 ; 1882, **93,** 67, 217, 591.

[3] *e.g.* German Patents 92,789, 95,644, 96,145, 102,364, 107,225, 108,075, 131,980, 214,783, 224,388.

Detection. Codeine is distinguished from morphine by the differences in solubility recorded above, by giving no coloration with ferric chloride solution ; a yellow, not a reddish, solution with nitric acid ; and a blue, not a brown, tint when warmed with sulphuric acid. Sulphuric acid containing a trace of selenious acid produces a green coloration, changing to blue and back again to green.

For conversion of codeine into apo-ψ-codeine *see* p. 262.

Apocodeine " obtained by the action of zinc chloride on codeine is, according to Dott,[1] a mixture of chlorocodeide, apomorphine, amorphous bases and unchanged codeine. A number of homologues of codeine have been prepared by the alkylation of morphine, for example ethylmorphine, which, in the form of the hydrochloride, is known and used in medicine under the name " dionin " (colourless, bitter, microcrystalline powder, m.p. 122°–125°) and benzylmorphine, the hydrochloride of which is known as " peronin." Acyl derivatives have also been used as substitutes for morphine, *e.g.*, diacetylmorphine is the drug known as " heroin," and patents for other derivatives of these two kinds are numerous.

Isomerides of Morphine and Codeine. When morphine is heated with phosphorus trichloride or tribromide, the alcoholic hydroxyl group (*see* p. 267) is replaced by the halogen, forming chloromorphide and bromomorphide respectively. Both these substances when boiled with water yield a mixture of isomerides of morphine, two isomerides, α- and β-*iso*morphine, being common to both mixtures, three α-, β- and γ- (or *iso*, β-*iso*, and *neoiso*) being formed in all.

In like manner, there are formed from bromocodeide and chlorocodeide α-, β- and γ-*iso*codeines, which can also be obtained from the corresponding *iso*-morphines by methylation, and are better known under the names *iso*codeine, *allo*-ψ-codeine and ψ-codeine (*neoiso*codeine) respectively. These four isomerides in each case are stereoisomeric pairs, and the pairs differ from each other in the position of the alcoholic hydroxyl group, this being at 6 (*see* formula, p. 273) in the parent alkaloids and the α-isomerides, and at 8 in the β- and γ-forms. These isomerides in turn give rise to a series of four methylmorphimethines also existing in two pairs, which are structurally different, and the two members of the first pair are each

[1] *Pharm. Journ.* 1891 [iii], **21**, 878, 916, 955, 996. *Cf.* Matthiessen and Burnside, *Annalen*, 1871, **158**, 131 ; Merck, *Arch. Pharm.* 1891, **229**, 161 ; Göhlich, *ibid.* 1893, **231**, 235 ; Knorr and Roth, *Berichte*, 1907, **40**, 3356.

convertible into a second form by the action of alcoholic potash α- into β-, and γ- into δ-. The principal facts [1] about these three series of isomerides are assembled in the following table :

	Morphine.	α-*iso*morphine.	β-*iso*morphine.	γ-*iso*morphine.
M.p. . . .	253°	247°	182°	278°
$[a]_D$ . . .	— 133°	— 167°	— 216°	— 94°
Methylation product.	Codeine.	*iso*Codeine.	*allo*-ψ-Codeine.	ψ-Codeine.
M.p. . . .	155°	172°	Oil.	181°
$[a]_D$ . . .	— 135°	— 155°	— 228°	— 94°
Oxidation product.	Codeinone.		ψ-Codeinone.	
M.p. . . .	187°		174°	
$[a]_D$ . . .	— 205°		— 25°	
Exhaustive methylation product.	3 : 4 : 6-trimethoxy-phenanthrene.		3 : 4 : 8-trimethoxy-phenanthrene.	
	m.p. $[a]_D$	m.p. $[a]_D$	m.p. $[a]_D$	m.p. $[a]_D$
Methylation of the isomeric codeines gives the primary methyl-morphimethines,	α 119°, — 214°	γ 166°, + 65°	ζ oil, —178° (both stable	ε 130°, —120° to alkali)
which by action of alcoholic potash yield the secondary methylmorphimethines.	β 134°, + 438°	δ 113°, + 284°	—	—

Neopine. This alkaloid, described as amorphous, and readily soluble in water, alcohol, ether, chloroform or benzene, was discovered by T. and H. Smith in the final mother liquors obtained in the extraction of opium alkaloids, and has been examined by Dobbie and Lauder.[2] The salts crystallise well, the hydrobromide being sparingly soluble in water, from which it separates in hard prismatic crystals $[\alpha]_D^{20} + 17 \cdot 2°$ in water. The alkaloid contains one methoxyl group and behaves as a tertiary base with methyl iodide. It gives colour reactions and an absorption spectrum similar to those of codeine, and appeared to be a hydroxycodeine, though it is not identical with Ach and Knorr's hydroxycodeine (*see* p. 272). Accord-

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[1] For a selected bibliography of this subject, *see* Gulland and Robinson, *Trans. Chem. Soc.* 1923, **123,** 996 ; *see also* Speyer and Krauss, *Annalen,* 1923, **432,** 233.

[2] *Trans. Chem. Soc.* 1911, **99,** 34.

ing to Robinson and van Duin,[1] it has now been crystallised and found to be an isomeride of codeine.

Thebaine, $C_{19}H_{21}O_3N$. This base, which occurs in opium to the extent of 0·1 to 1 per cent., was first obtained by Thiboumery,[2] who regarded it as isomeric with morphine and named it "paramorphine," and was subsequently examined by Kane,[3] who first called it "thebaine," and by Anderson,[4] who assigned to it the formula given above. It remains in the mother liquor after the removal of morphine and codeine hydrochlorides, and Hesse's method of preparing it from this source has been described (p. 258). The acid tartrate thus obtained is crystallised from hot water, and the alkaloid regenerated from it is recrystallised from dilute alcohol, from which it separates in leaflets, or from dry alcohol, in prisms, m.p. 193°, $[\alpha]_D^{15}$ — 218·6° in alcohol. It is readily soluble in alcohol, chloroform or benzene, less so in ether, and almost insoluble in cold water, but sparingly so in ammonia or lime-water. Thebaine behaves as a monoacidic base. The hydrochloride, $B.HCl.H_2O$, forms large rhombic prisms, $[\alpha]_j$ — (168·32° — 2·33c), soluble in 15·8 parts of water at 10°. The salicylate is sparingly soluble in water, and may be used for the separation of thebaine from other opium alkaloids.[5] Thebaine gives a blood-red coloration with sulphuric acid, which turns orange-yellow and eventually olive-green on warming.[6]

CONSTITUTION OF MORPHINE, CODEINE AND THEBAINE

Morphine has been the subject of investigation almost continuously since its discovery in 1804, with the result that the experimental evidence available for the discussion of its constitution is so voluminous as to preclude anything like a full account of it being given within the moderate compass available in a text-book dealing with alkaloids as a whole. It is necessary, therefore, to restrict attention to those lines of investigation which have brought out the peculiarities of this small but important group of alkaloids. It is now fairly certain that these three alkaloids are not *iso*quinoline derivatives, and do not belong to the group now under discussion,

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[1] Preliminary announcement by Gulland and Robinson, *Trans. Chem. Soc.* 1923, **123**, 996.

[2] *Annalen*, 1835, **16**, 38.

[3] *Ibid.* 1836, **19**, 9.

[4] *Ibid.* 1853, **86**, 184.

[5] Plugge, *Rec. trav. chim.* 1887, **6**, 157.

[6] For other colour reactions of thebaine, *see* Reichard, *Pharm. Centr.-Halle.* 1906, **47**, 623 (*Chem. Soc. Abstr.* 1906 [ii], 909).

but they can be regarded as divergences or developments from this type. Further, they readily yield *iso*quinoline alkaloids, and their associates in nature belong to this group, so that there are ample reasons for not treating them in a separate class.

The three alkaloids all behave as tertiary bases. Morphine contains two hydroxyl groups; one of these is phenolic and the other is present as a secondary alcohol group. On methylation the phenolic hydroxyl is converted into methoxyl, and codeine results. On oxidation codeine is transformed into codeinone by conversion of the secondary alcohol group into a carbonyl group, and when thebaine is boiled with normal sulphuric acid for a few minutes, it is hydrolysed into codeinone and methyl sulphate, and in other ways thebaine has been shown to contain two methoxyl groups. The relationship between the three alkaloids is, therefore, very close, and may be illustrated by the following slightly extended formulæ:

$$\begin{array}{cc} \left.\begin{array}{c} HO \\ CHOH \end{array}\right\rangle C_{16}H_{16}ON & \left.\begin{array}{c} CH_3O \\ CHOH \end{array}\right\rangle C_{16}H_{16}ON \\ \textit{Morphine} & \textit{Codeine} \\[2em] \left.\begin{array}{c} CH_3O \\ CO \end{array}\right\rangle C_{16}H_{16}ON & \left.\begin{array}{c} CH_3O \\ C.OCH_3 \end{array}\right\rangle C_{16}H_{15}ON \\ \textit{Codeinone} & \textit{Thebaine} \end{array}$$
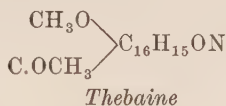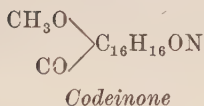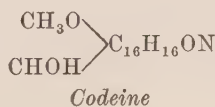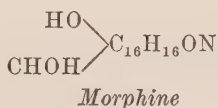
Codeine is therefore a methyl ether of morphine, whilst thebaine is a methyl ether of an enolic form of codeinone. There has been much discussion as to the function of the third or "indifferent" oxygen in the three alkaloids, and its nature has only been disclosed by a study of the degradation products of the alkaloids.

The three alkaloids all yield characteristic products on treatment with hydrochloric acid. In this way morphine yields apomorphine (described on p. 261), by loss of the elements of water; codeine also yields apomorphine, accompanied by other products, but thebaine yields, with dilute hydrochloric acid, thebenine, and, with strong hydrochloric acid, morphothebaine. These two are respectively secondary and tertiary bases, so that presumably in the formation of thebenine a heterocyclic ring has been opened and a tertiary nitrogen converted into a secondary nitrogen, : NCH_3 into . $NHCH_3$. Further, thebenine and morphothebaine are both isomeric with codeinone, and, as the latter can also be converted into thebenine and morphothebaine by the action of hydrochloric acid at appro-

priate strengths and temperatures, it seems clear that in the action of hydrochloric acid on thebaine the latter loses methyl chloride and produces codeinone, which is then, by further action of this acid, transformed into thebenine and morphothebaine. Codeinone thus becomes a very important substance in the chemistry of this sub-group. The relationships thus far established may be summarised thus :

$$
\begin{array}{c}
\text{HO}\!>\!\!\diagdown \\
\text{CHOH}\!\diagup\!\!C_{16}H_{16}ON \xrightarrow{\qquad} \quad
\text{HO}\!>\!\!\diagdown \\
\text{CH}\!\diagup\!\!C_{16}H_{15}ON \xleftarrow{\qquad} \quad
\text{CH}_3\text{O}\!>\!\!\diagdown \\
\text{CHOH}\!\diagup\!\!C_{16}H_{16}ON
\end{array}
$$

$Morphine$　　　　$Apomorphine$　　　　$Codeine$

$$
\text{CH}_3\text{O}\!>\!\!C_{16}H_{15}ON
$$
$\qquad\qquad$ C.OCH$_3$
$Thebaine$ $\longrightarrow$

$$
\text{CH}_3\text{O}\!>\!\!C_{16}H_{16}ON
$$
CO
$Codeinone$

$$
\text{CH}_3\text{O}\!>\!\!C_{16}H_{15}ON
$$
C.OH
$Morphothebaine$

$$
\text{CH}_3\text{O}\!>\!\!C_{16}H_{14}ONH
$$
C.OH
$Thebenine$
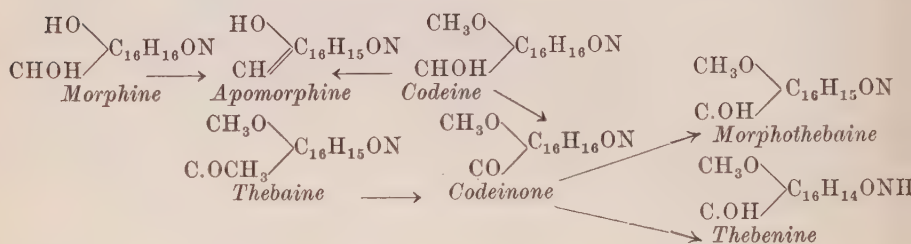
The conversion of thebaine (and codeinone) into two isomeric bases, one secondary and one tertiary, but each containing one methoxyl group and two hydroxyl groups, is an example of a change now believed to be due to intramolecular migration, which is peculiarly common to this sub-group of alkaloids, and it is the necessity of explaining the aptitude of the group for this type of change that has been the chief obstacle in designing formulæ to explain the reactions of its members. This difficulty is found perhaps in its worst form in the case of the methylation products of codeine, the methylmorphimethines, of which six isomerides are known, and in the products formed by the action of phosphorus halides on morphine and codeine. The characters, mode of formation and reactions of these products are summarised in the table on p. 265.

When α-methylmorphimethine is warmed with hydrochloric acid or acetic anhydride, it is partly converted into β-methylmorphimethine and partly decomposed into two new substances, one basic and the other neutral,[1] thus :

$$
\begin{array}{c}
\text{CH.OH}\!>\!\!\diagdown \\
\text{CH}_3\text{O}\!\diagup
\end{array}\!\!C_{16}H_{15}O:NCH_3 \rightarrow
\begin{array}{c}
\text{CH}\!>\!\!\diagdown \\
\text{CH}_3\text{O}\!\diagup
\end{array}\!\!C_{13}H_7.OH + CH_2OH.CH_2.N(CH_3)_2
$$

$α\text{-}Methylmorphimethine$　　$Methylmorphol$　　　$Hydroxyethyldimethylamine$
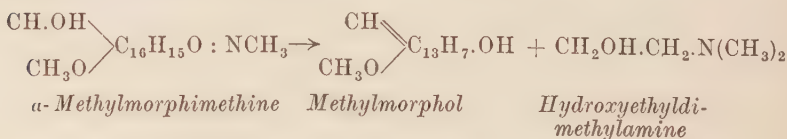
Consideration of its reactions led Vongerichten to formulate

[1] Vongerichten, *Berichte*, 1886, **19**, 792 ; 1898, **31**, 2924 ; 1899, **32**, 1521. *Cf.* Knorr, *ibid.* 1889, **22**, 185, 1113 ; 1894, **27**, 1148 ; 1904, **37**, 3494.

methylmorphol as 3-methoxy-4-hydroxyphenanthrene,[1] and this representation was proved to be correct by Pschorr and Sumuleanu's synthesis of 3 : 4-dimethoxyphananthrene,[2] which proved to be identical with the methyl ether of methylmorphol. When either α-methylmorphimethine methohydroxide or its β-isomeride is heated alone a decomposition similar to the foregoing takes place, with, however, an interesting variation thus : [3]

$$\begin{array}{c} \text{CHOH} \\ \diagdown \\ \text{CH}_3\text{O} \diagup \end{array} \text{C}_{16}\text{H}_{15}\text{ON} \begin{array}{c} \diagup \text{OH} \\ \diagdown \\ (\text{CH}_3)_2 \end{array} \rightarrow \quad \text{CH}_3\text{O}.\text{C}_{14}\text{H}_7\text{O} \; + \; \text{N}(\text{CH}_3)_3 \; + \; \text{C}_2\text{H}_4 \; + \; 2\text{H}_2\text{O}$$

<div align="center">a-<i>Methylmorphimethine-   Methylmorphenol   Trimethyl-   Ethylene</i>
<i>methohydroxide   amine</i></div>
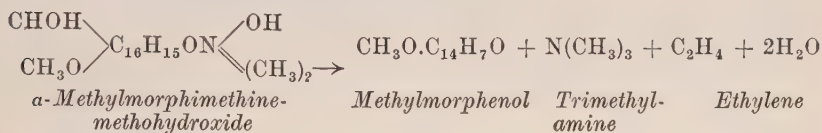
On fusion with potash, methylmorphenol is converted into 3 : 4 : 5-trihydroxyphenanthrene, and the constitution of this has been clearly established by its conversion into the trimethyl ether, which is identical with 3 : 4 : 5-trimethoxyphenanthrene synthesised by Pschorr.[3] The " indifferent " oxygen of morphine and codeine is, therefore, probably the source of the hydroxyl group in position 4 in these phenanthrene derivatives produced by the degradation of codeine.

A similar reaction takes place with codeinone, $\text{C}_{18}\text{H}_{19}\text{O}_3\text{N}$ (m.p. 185°–186°, $[\alpha]_D^{15} - 205°$ in alcohol), the ketone corresponding to the secondary alcohol codeine (see p. 267), which with acetic anhydride yields the diacetyl derivative of a dihydroxymethoxyphenanthrene, which on replacement of the two acetoxy groups by methoxyl groups yields methylthebaol [4] ; the latter had already been synthesised by Pschorr, Seydel and Stöhrer,[5] and shown to be 3 : 4 : 6-trimethoxyphenanthrene. Thebaïne under the action of acetic anhydride at 100° [6] yields 4-acetylthebaol and the diacetyl derivative of methylhydroxyethylamine. A similar reaction takes place with benzoyl chloride at 0°.[7] These are typical cases of a reaction general in this sub-group, which has proved very useful in deciding the orientation of the side-chains in relation to the phenan-

[1] Berichte, 1897, **30**, 2439 ; 1898, **31**, 3198 ; 1900, **33**, 352, 1824 ; 1901, **34**, 2722.

[2] Ibid. 1900, **33**, 1810. For a synthesis of morphol, see Smith, Trans. Chem. Soc. 1916, **109**, 568 ; Barger, ibid. 1918, **113**, 218.

[3] Vongerichten, Berichte, 1896, **29**, 67 ; 1906, **39**, 1718 ; Pschorr, Annalen, 1912, **391**, 40.

[4] Knorr, Berichte, 1903, **36**, 3074.

[5] Ibid. 1902, **35**, 4400.

[6] Freund, ibid. 1897, **30**, 1634 ; 1899, **32**, 168. Cf. Knorr, ibid. 1904, **37**, 3499.

[7] Pschorr and Haas, ibid. 1906, **39**, 16.

threne skeleton common to all three alkaloids and their near relatives. The characters of the phenanthrene derivative produced by the degradation of the more important members of the sub-group are summarised in the following table :

Alkaloid.		Phenanthrene Derivative.
I. Morphine	. .	⌠3-Methoxy - 4 - hydroxyphenanthrene or
Codeine	. .	⌡ 3-methoxy-4 : 5-oxyphenanthrene.
Thebaine	. .	3 : 6-Dimethoxy-4-hydroxyphenanthrene
Codeinone	. .	3-Methoxy-4 : 6-dihydroxyphenanthrene.
II. Apomorphine	.	3 : 4-Dimethoxy-8-vinylphenanthrene.
Morphothebaine	.	3 : 4 : 6-Trimethoxy-8-vinylphenanthrene
III. β- or γ-isoMorphine.		
↓		
ψ-Codeine	.	3-Methoxy-4 : 8-dihydroxyphenanthrene.
↓		
ψ-Codeinone	.	
IV. Thebenine	. .	3 : 4 : 8-Trimethoxy-5-vinylphenanthrene

The basic hydrolytic product is invariably trimethylamine in the fully methylated product ultimately hydrolysed, accompanied sometimes by ethylene, but occasionally the two carbon atoms with which the nitrogen atom is associated remain attached to the phenanthrene nucleus as a vinyl group (cases 5, 6, 10, in above table), but, as already pointed out, thebaine and α-methylmorphimethine, on hydrolysis by hydrochloric acid or acetic anhydride, yield hydroxyethyldimethylamine.   The exact nature of the primary basic product of hydrolysis was a matter of much importance in connection with the earliest attempts to assign a formula to morphine, since the " indifferent " oxygen was at first believed to form part of the : N.Ċ.Ċ. chain, detached from the phenanthrene skeleton in this change, and it was fully investigated by Knorr,[1] who showed that hydrochloric acid decomposes methylmorphimethine first into methylmorphol (3-methoxy-4-hydroxyphenanthrene) and chloroethyldimethylamine : the latter being then converted by the alkali added in isolating it into a mixture of tetramethylethylenediamine and hydroxyethyldimethylamine.[1]   Knorr first suggested that the production of these substances implies the presence in the methine base of the complex, $.CH_2 : CH.N(CH_3)_2$, which may combine with hydrogen chloride to give chloroethyldimethylamine,

[1] Berichte, 1904, 37, 3494, 3507.

$CH_2Cl.CH_2.N(CH_3)_2$, or with alcohol (when the latter is used at 160° to effect the decomposition) to form dimethylaminoethyl ether, $C_2H_5O.CH_2.CH_2.N(CH_3)_2$.

It follows from the evidence thus obtained, that morphine and consequently codeine and thebaine, must be built up from the complex $.CH_2.CH_2.\dot{N}.CH_3$, and a phenanthrene skeleton capable of yielding such derivatives as the following : [1]

Morphol

Morphenol

Thebaol

3-Methoxy : 4 : 6-dihydroxy-phenanthrene from codeinone
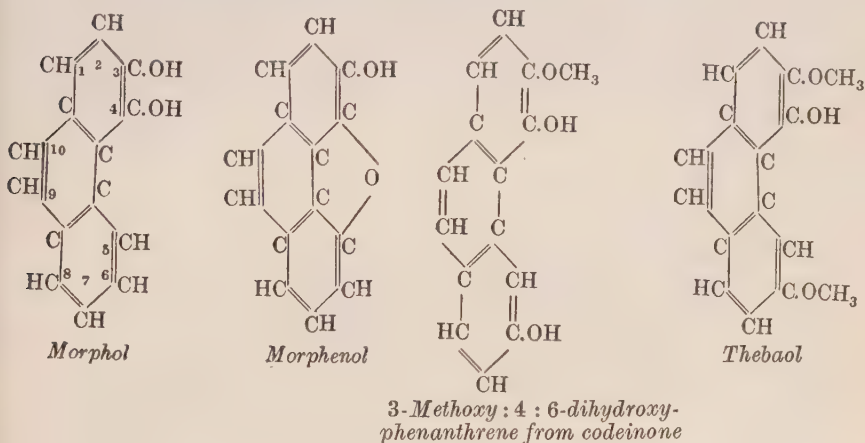
Referring to the table on p. 270, it will be seen that in type I positions 3 and 4 are always occupied by hydroxyl or methoxyl, and in the cases of codeinone methiodide and thebaine, which are easily hydrolysed, position 6 is similarly occupied. It is also possible to get from thebaine a substance thebenol constituted in an analogous manner to morphenol. There can be little doubt, therefore, that so far as the oxygen atoms are concerned in the four alkaloids included in this type, the phenolic hydroxyl in morphine is at position 3, the indifferent oxygen forms a furan ring between positions 4 and 5, and the alcoholic hydroxyl is at 6. Codeine differs from morphine in having a methoxyl at 3, and codeinone from codeine by the conversion of a .CHOH group into .CO. at 6, whilst thebaine differs from codeinone by the replacement of CO at 6 by $C.OCH_3$. Comparing this type with III, it will be seen that β- and γ-iso-morphines and ψ-codeine, and consequently ψ-codeinone, which is related to them in the same way as codeinone to morphine and codeine, differ from their isomerides of type I by the wandering of the hydroxyl group from position 6 to position 8. From none of these

[1] *Cf.* Knorr and Pschorr, *Berichte*, 1905, **38**, 3176.

seven alkaloids or their isomerides has it been possible to obtain directly substituted vinylphenanthrenes, and thus to secure direct evidence of the mode of attachment of the ethanamine chain to the phenanthrene nucleus. In the remaining two types II and IV, this has been possible, and in type II it is clear that in apomorphine and morphothebaine the carbon end of the ethanamine chain must be at 8, and the hydroxyl or methoxyl groups at 3 and 4 and at 3 : 4 : 6- respectively, so that there has been no wandering of the labile hydroxyl. In thebenine, on the contrary, the carbon end of the ethanamine chain must be at 5 and the hydroxyl originally at 6 in thebaine has wandered to 8. Except in the case of thebenine and its homologues and the methylmorphimethines, which are all produced by fission of the heterocyclic ring, the attachment of the nitrogen end of the ethanamine chain to the phenanthrene nucleus is assumed with good reason to be at 9, since hydroxycodeine, obtained by the oxidation of codeine with chromic acid,[1] on con- version into the methine base and treatment of the latter with acetic anhydride yields a methoxydiacetoxyphenanthrene, which on oxidation with chromic acid yields acetylmethylmorpholquinone identical with that obtained by oxidising the 4-acetyl-3-methyl- morphol produced by the action of acetic anhydride on methyl- morphimethine, whence it follows that the new hydroxyl group must be in position 9 or 10,[2] of which 9 is the more likely.

Pschorr and his collaborators have assigned formulæ to apo- morphine,[3] morphothebaine [4] and thebenine,[4] which are now generally accepted.
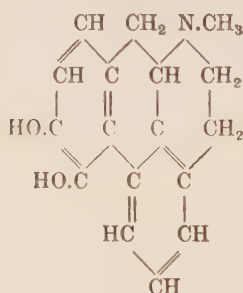
Apomorphine (Pschorr)   *Morphothebaine* (Pschorr)
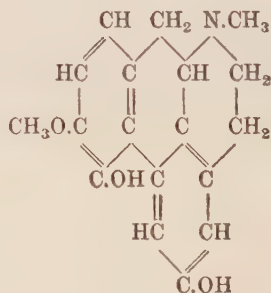
[1] Ach and Knorr, *Berichte*, 1903, **36**, 3068.

[2] Knorr, with Schneider and Horlein, *ibid.* 1906, **39**, 1414, 3252.

[3] Pschorr, Jaeckel and Fecht, *ibid.* 1902, **35**, 4377.   *Cf.* 1906, **39**, 3124 ; 1907, **40**, 1984, 1995, 1998, 2044 ; 1912, **45**, 2212.

[4] *Annalen*, 1910, **373**, 51, 64, 69, 75 ; 1911, **382**, 50.   *Cf. Berichte*, 1904, **37**, 2780 ; and Freund, *ibid.* 1899, **32**, 168.
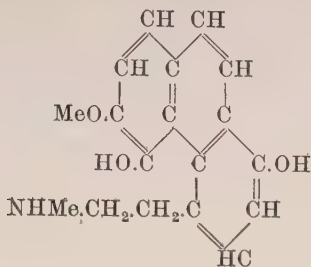
Thebenine (Pschorr)

With regard to the three parent alkaloids, the most doubtful point remains the position at which the carbon end of the ethanamine chain is attached to the phenanthrene nucleus, and the numerous formulæ proposed since 1905 are mainly expressions for different modes of attachment of this side-chain. Taking the general formula below, in which X and X′ represent known positions for hydroxyl or methoxyl groups in the three alkaloids, Pschorr [1] proposed to join
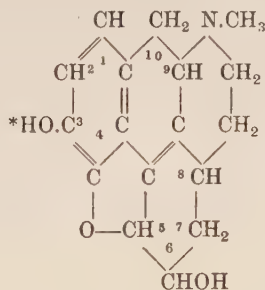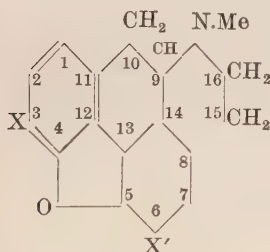
Morphine (Pschorr)

* This H is replaced by CH_3 in codeïne.

15 to 8, thus developing formulæ for morphine, codeine and thebaine, from his representation of apomorphine. The principal objection taken to this formula was that position 8 being occupied left no room for the migration of the hydroxyl from 6 to 8, such as takes place in β- and γ-*iso*morphine and ψ-codeine, since these yield ψ-codeinone, which can be degraded to 3 : 4 : 8-trihydroxyphenanthrene (p. 270). Knorr and Horlein [2] overcame this particular

[1] Pschorr, Jaeckel and Fecht, *Berichte*, 1902, **35**, 4377. *Cf.* 1905, **38**, 3160 ; 1906, **39**, 3214 ; 1907, **40**, 1984, 1995, 1998, 2004, 3652 ; 1912, **45**, 2212.

[2] *Ibid.* 1906, **39**, 1414 ; 1907, **40**, 3341. *Cf.* Faltis, *Pharm. Post.* 1906, **39**, 497.

difficulty by assuming that carbon atom 15 was joined to 5, and though other suggestions have been made, for example by Freund [1] (ethanamine bridge from 5 to 8), Bucherer [2] and Wieland and Kappelmeier,[3] Knorr and Horlein's formula has until recently been generally accepted.
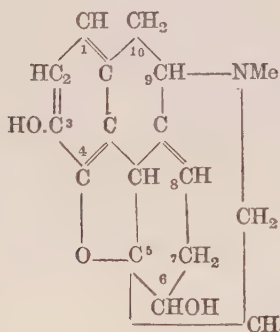
Morphine (Knorr and Horlein)   *Methylmorphimethine*
                                        (Knorr and Horlein)
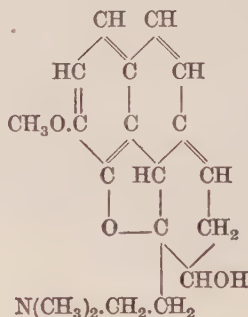
Knorr and Horlein's formula requires one ethylenic linkage in ring III for morphine and codeine and two for thebaine, and there is little or no experimental evidence to support this view. It is true that these alkaloids can be reduced, but the reduction usually affects the oxygen in the furan ring and is not mere addition of hydrogen to one or more ethylenic linkages.[4] Further, it is unlikely that if codeine contained a double bond it would merely undergo conversion of the .CHOH group in position 6 to .CO. (codeinone) by the action of potassium permanganate in acetone. Von Braun [5] has shown that when a double bond is present in the $\beta\gamma$-position with respect to nitrogen, such as is assumed in the Knorr and Horlein formulæ for these alkaloids, rupture of the chain at the N atom usually occurs when cyanogen bromide reacts with the substance

[1] *Berichte,* 1905, **38**, 3234.
[2] *Journ. prakt. Chim.* 1907 [ii], **76**, 428.   *Cf.* Knorr, *Berichte,* 1907, **40**, 4891.
[3] *Annalen,* 1911, **382**, 306.
[4] Oldenburg, German Patent 260,233 (*Chem. Soc. Abstr.* 1913 [i], 1093).   *Cf.* von Braun, *Berichte,* 1914, **47**, 2312 ; and Freund, *Berichte,* 1916, **49**, 1287 ; 1920, **53**, 2250, German Patent 338,147 (*Chem. Soc. Abstr.* 1921 [i], 803) ; and Mannich and Löwenheim, *Arch. Pharm.* 1920, **258**, 295.
[5] Von Braun, Kruber and Aust. *Berichte,* 1914, **47**, 2312 ; 1916, **49**, 750, 977 ; 1917, **50**, 43 ; 1918, **51**, 96, 255 ; 1919, **52**, 1999 ; 1922, **55**, 3536 ; 1923, **56**, 538.

rather than elimination of the CH_3 from the $.NCH_3$ group. Applying this method, he found that whilst morphine and codeine were converted into N-demethylated bases, thebaine combined directly with cyanogen bromide, indicating that there was no double bond in positions 8—13, or 8—14, in codeine and morphine, but that such a bond might exist in thebaine, and does exist in apomorphine. On these grounds he suggested a modification of Knorr and Horlein's formula for morphine and codeine by introducing a bridge between positions 6 and 8.

Similarly Gadamer [1] threw doubt on the view that the nitrogen end of the ethanamine chain is attached at position 9, and proposed a modified form of Freund's formula (bridge 5 to 8). Faltis,[2] on the other hand, sees no objection to the retention of the ethylenic linkage in morphine and codeine, but proposes a new formula in which the indifferent oxygen is joined to 4 and 8, but is otherwise like Knorr and Horlein's. This modification simplifies many of the difficulties of the latter formula. Somewhat later Freund and Speyer also came to the conclusion that Knorr and Horlein's formula is untenable mainly on the ground that phenyldihydrothebaine [3] does not reduce in the manner expected. This substance, which is obtained by the action of magnesium phenyl bromide on thebaine, is more stable to acids than thebaine, and, therefore, more amenable to treatment by ordinary reduction methods, yet it is not reducible by electrolytic methods, and when acted upon by hydrogen in presence of colloidal palladium is converted into a secondary base,
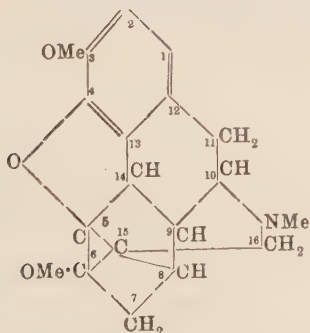
Thebaine
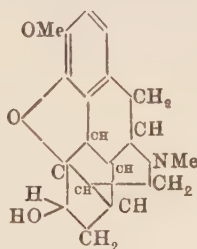
Codeine (OMe replaced by OH = Morphine)

[1] *Zeit. angew. Chem.* 1913, **26,** 625.
[2] *Arch. Pharm.* 1917, **255,** 89 ; *Monats.* 1923, **43,** 255, 377 ; [with Sappan] *Pharm. Monats.* 1923, **4,** 189.
[3] *Berichte,* 1905, **38,** 3248.

phenylthebainimine, owing to the opening of the ring containing nitrogen, and on this and other grounds they suggested for discussion the preceding formulæ for thebaine and codeine,[1] which it will be seen are modifications of Knorr's formulæ designed to do away with the ethylenic linkages.

Gulland and Robinson [2] have recently reviewed the evidence available regarding the structure of morphine and codeine, and have come to the conclusion that the data on which Pschorr's formula (p. 273) is based have been too lightly dismissed, and they suggest that the ethanamine chain is associated with the phenanthrene skeleton by the bridge 8–15–13 (formula I), or 8–15–14 (formula II) of which the authors prefer (I).
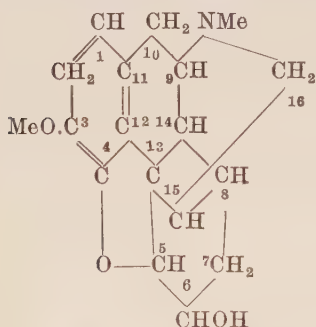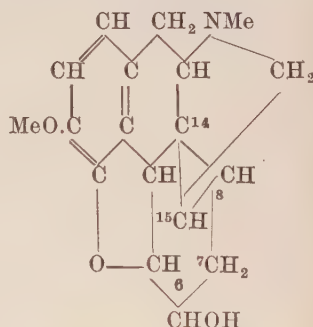
(I) *Codeine* (Gulland and Robinson)   (II) *Codeine* (Gulland and Robinson)

The principal reason adduced for putting forward these formulæ is that they explain why in morphine and its allies the formation of phenanthrene derivatives and an aminoethanol derivative always takes place simultaneously.   Such a change cannot occur except under conditions which will add a hydrogen atom at positions 13 or 14.   Thus the conversion of α-methylmorphimethine into

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[1] *Berichte,* 1916, **49,** 1287. For applications of the formula *see Journ. prakt. Chim.* 1916 [iii], **94,** 135 (7-hydroxycodeinone) ; *ibid.* 1920 [ii], **101,** 1 (tetrahydrodeoxycodeines) and compare *Berichte,* 1920, **53,** 2250 ; 1921, **54,** 1519, 2647, 2976 ; 1922, **55,** 1329 ; *Annalen,* 1922, **430,** 1, in which Freund or Speyer and collaborators deal mainly with reactions designed to test this and Knorr's formula.

[2] *Trans. Chem. Soc.* 1923, **123,** 985, 998.   The former paper contains a useful selected bibliography of literature on morphine, codeine and thebaine.   For another useful review *see* Faltis, *Arch. Pharm.* 1917, **255,** 85.

acetylmethylmorphol and acetoxyethyldimethylamine (p. 268) is regarded as taking place in the following way :

a-Methylmorphimethine
(G. and R.)

Intermediate product
+
AcO.CH$_2$.CH$_2$.NMe$_2$

*Acetylmethyl-
morphol*
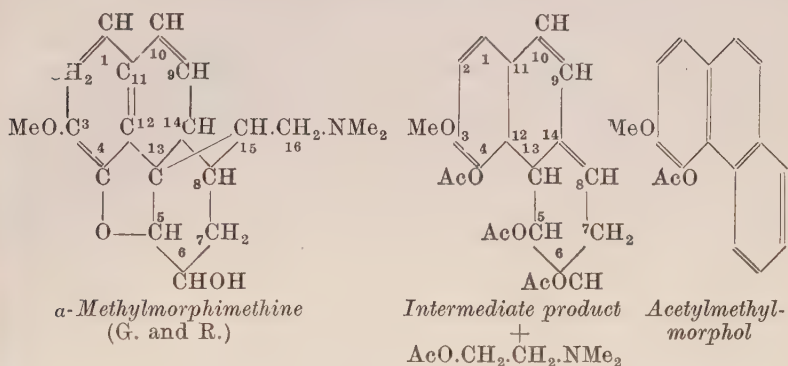
The formula also explains satisfactorily the formation of six isomeric methylmorphimethines. In four of these, viz., α-, β-, γ- and δ- the hydroxyl group is known to be at position 6, and in ε- and ζ- it is known to be at 8.   α- is readily convertible into β- and γ- into δ- by the action of alcoholic alkali, but the ε- and ζ- forms are not interconvertible, because, it is argued, there is less tendency for a bridge to break down when the resultant product is unable to form a conjugated system of two ethylene linkages such as is formed in the case of the β-isomeride.

β-Methylmorphimethine (G. and R.)

ε- and ζ-Methylmorphimethine
(G. and R.)
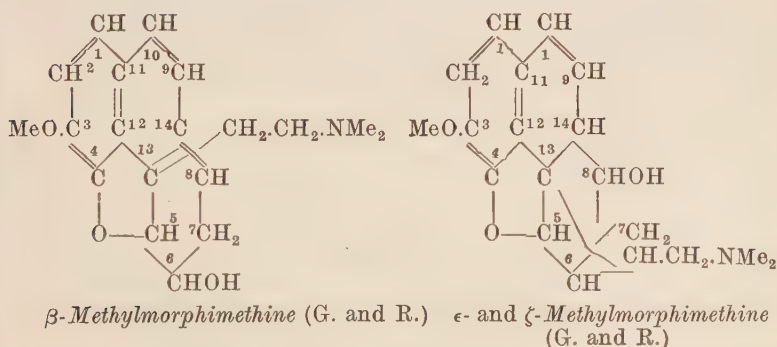
The formula explains equally well other typical reactions of this group of alkaloids, and numerous examples of these are given in the original paper. A formula for thebaine on this basis has not yet been put forward, but the authors show that the new formula applied to codeinone readily affords an explanation of the conversion

of this substance into morphothebaine and of ψ-codeinone into thebenine.

CH₂ NMe structures...
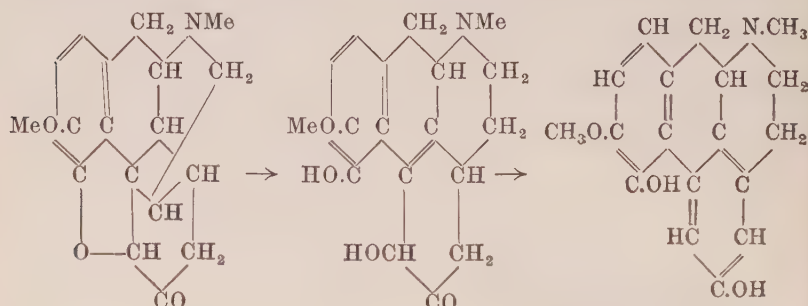
Codeinone (G. and R.)   *Intermediate Product* (G. and R.)   *Morphothebaine* (Pschorr)
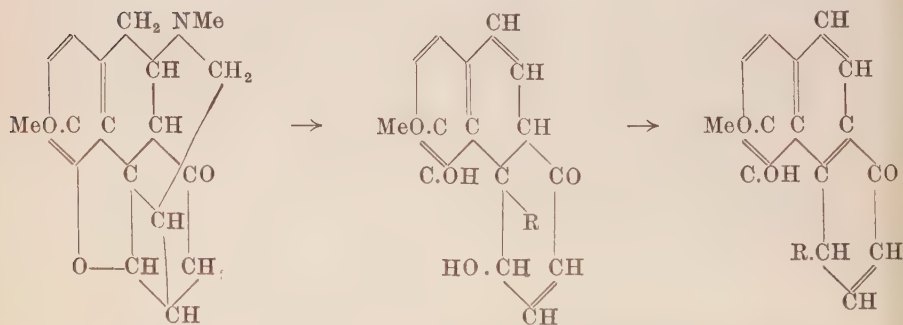
ψ-*Codeinone* (G. and R.)   *Intermediate products* (G. and R.) $\quad R = .CH_2.CH_2.NHMe$
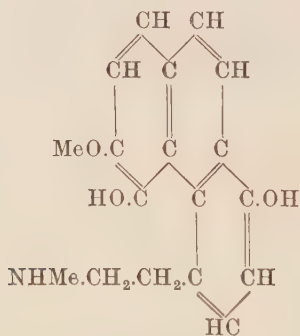
Thebenine (Pschorr ; *cf.* p. 273)

One of the most attractive features of this new formula is that it brings morphine, codeine and thebaine into close relationship once

more with other alkaloids occurring in the same series of plants, an advantage which it shares with Pschorr's now discarded formula.

NARCOTINE-PAPAVERINE SUB-GROUP

Narcotine, $C_{22}H_{23}O_7N$. This alkaloid was obtained in an impure state by Derosne in 1803, but was first definitely isolated by Robiquet in 1817, who assigned to it the formula, $C_{23}H_{25}O_7N$, which was changed by Matthiessen and Foster [1] to that now in use. When opium is extracted with water to obtain morphine and codeine, the narcotine remains largely in the insoluble residue, from which it may be extracted by ether or benzene or by dilute hydrochloric acid. From the solution of narcotine hydrochloride so obtained, the alkaloid may be precipitated by sodium bicarbonate. The base obtained in either of these ways may be recrystallised from boiling alcohol. The quantity present in opium varies from 1 to 9 per cent., being largest in Indian and Persian opiums.

Narcotine crystallises from alcohol in long colourless needles, m.p. 176°, $[\alpha]_j$ — 207·35°, $[\alpha]_D$ — 198·0° in chloroform, + 50° in 1 per cent. hydrochloric acid [2]; it is nearly insoluble in water, sparingly so in cold 85 per cent. alcohol (1 in 100) or ether (1 in 166 at 16°), readily in benzene, acetone or ethyl acetate ; insoluble in cold alkalis or ammonia, but soluble in hot alkalis or " milk of lime." With acids it forms unstable salts that are dissociated by water, so that the alkaloid can often be extracted by indifferent solvents from its solutions in dilute acids. The salts are dextrorotatory.

The alkaloid dissolves in sulphuric acid with a greenish colour, changing to red and reddish violet on warming or long standing. With sulphuric acid containing a trace of nitric acid a deep red colour is produced. According to Labat [3] a solution of narcotine in sulphuric acid gives, on warming with gallic acid, a deep blue coloration, due to the liberation of opianic acid. This reaction is also given by hydrastine.

Constitution. Narcotine is a weak, monoacidic, tertiary base, and yields an oily methiodide, which is converted by silver chloride and caustic soda into narceine. [4] It contains three methoxyl groups, and when heated in closed tubes with dilute hydrochloric acid,

[1] *Annalen,* 1862, *Suppl.* **1,** 330 ; 1863, **2, 377.**

[2] *Cf.* Annett, *Trans. Chem. Soc.* 1923, **123,** 378.

[3] *Bull. Soc. chim.* 1909 [iv], **5,** 742, 743.

[4] Freund and Frankforter, *Annalen,* 1893, **277,** 35, 48. *Cf.* Roser, *ibid.* 1888, **247,** 167.

furnishes the following series of demethylated derivatives [1] : *dimethylnornarcotine*, $C_{19}H_{14}O_4N.OH(OCH_3)_2$, *methylnornarcotine*, $C_{19}H_{14}O_4N(OH)_2.OCH_3$, *nornarcotine*, $C_{19}H_{14}O_4N(OH)_3$.

When the alkaloid is heated with water at 150°, or boiled with dilute acids, it is hydrolysed into a basic substance, *hydrocotarnine*, and *opianic acid*. Similar decompositions are induced by acid oxidation or acid reduction, thus : (1) dilute nitric acid furnishes *opianic acid*, $C_{10}H_{10}O_5$, and *cotarnine*, $C_{12}H_{15}O_4N$; (2) nascent hydrogen gives *meconin*, $C_{10}H_{10}O_4$, and *hydrocotarnine*, $C_{12}H_{15}O_3N$. *Meconin*, $C_{10}H_{10}O_4$, is a constant constituent of opium from which it was isolated in 1832 by Dublanc, and has also been found in *Hydrastis canadensis*. It crystallises from water in prisms, m.p. 102°, is soluble in most organic solvents, and dissolves in alkaline solutions forming unstable salts of meconinic acid, $C_{10}H_{12}O_5$, of which it is the lactone and from which meconin is regenerated on addition of dilute mineral acids. It contains two methoxyl groups. The synthesis of meconin has been effected by Fritsch [2] from guaiacol as a starting-point.

Opianic acid, $C_{10}H_{10}O_5$, crystallises in prisms, m.p. 150°. Its constitution is clearly shown by the formation from it of protocatechuicaldehyde, carbon dioxide, and two molecular proportions of methyl iodide, when it is heated with hydriodic acid and by its conversion into hemipinic acid (3 : 4-dimethoxyphthalic acid) on oxidation, and into meconinic acid by reduction :

$$
\begin{array}{ccc}
\text{C.CHO} & \text{C.CH}_2\text{OH} & \text{C.CH}_2\text{O} \\
\text{CH}\quad\text{C.COOH} & \text{CH}\quad\text{C.COOH} & \text{CH}\quad\text{C}-\text{CO} \\
\text{CH}\quad\text{C.OCH}_3 & \text{CH}\quad\text{C.OCH}_3 & \text{CH}\quad\text{C.OCH}_3 \\
\text{C.OCH}_3 & \text{C.OCH}_3 & \text{C.OCH}_3 \\
\textit{Opianic acid} & \textit{Meconinic acid} & \textit{Meconin}
\end{array}
$$

By reduction
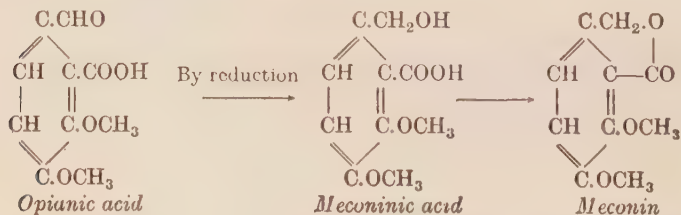
Hydrocotarnine, $C_{12}H_{15}O_3N.\frac{1}{2}H_2O$, the basic hydrolytic product of narcotine also occurs in opium.[3] It crystallises from alcohol in monoclinic prisms, m.p. 55°–56°, and yields well-crystallised salts, of which the hydrobromide, $B.HBr.1\frac{1}{2}H_2O$, m.p. 236°–237°, is sparingly soluble in water. On oxidation, hydrocotarnine is converted into cotarnine, and on reduction by sodium in alcohol it yields hydrohydrastinine.

[1] Matthiessen and Wright, *Annalen*, 1863, **2**, 377.
[2] *Ibid.* 1898, **301**, 351.
[3] Hesse, *Ibid.* 1871, *Suppl.* **8**, p. 326.

Cotarnine, $C_{12}H_{15}O_4N$. This base, first obtained by Wöhler [1] by the oxidation of narcotine with manganese dioxide in presence of sulphuric acid, is more conveniently prepared by oxidising narcotine [2] with dilute nitric acid. It crystallises from benzene in small needles, m.p. 132° (*decomp.*), is easily soluble in alcohol or ether, sparingly in cold water, and forms salts with mineral acids, losing at the same time a molecule of water; thus the hydrochloride has the composition, $C_{12}H_{13}O_3N \cdot HCl \cdot 2H_2O$, m.p. 197° (*decomp.*), and crystallises in pale yellow silky needles. This salt of cotarnine, under the name "stypticin," has come into use in medicine as a styptic. The phthalate is similarly used under the name "styptol." Cotarnine aurichloride forms golden-yellow plates, m.p. 136°–137°; the picrate crystallises in yellow needles, m.p. 143°.

Cotarnine behaves as a secondary base and reacts with methyl iodide to form cotarnine hydriodide and cotarninemethinemethiodide $C_{11}H_{11}O_4 \cdot N(CH_3)_3 \cdot I$. The latter with alkalis furnishes trimethylamine and *cotarnone*, $C_{11}H_{10}O_4$. This crystallises from alcohol in leaflets, m.p. 78°, with hydroxylamine gives cotarnonoxime, m.p. 130°–132°, and is oxidised by potassium permanganate to a mixture of cotarnic acid, $C_{10}H_8O_7$, and cotarnlactone, $C_{11}H_{10}O_6$. The former crystallises in needles, melting and passing into the anhydride at 178°, and when heated with concentrated hydrochloric acid loses a molecule of carbon dioxide, forming the methylmethylene ether of gallic acid (2-methoxy-3 : 4-dioxymethylenebenzoic acid). Cotarnlactone, brilliant leaflets, m.p. 154°, dissolves in alkaline liquids, forming salts of an unstable lactonic acid from which the lactone is readily regenerated. It furnishes cotarnic acid on further oxidation. On the basis of these results, Roser assigned the following formulæ to cotarnone and its oxidation products. [3]

Cotarnone — Cotarnlactone — Cotarnic acid
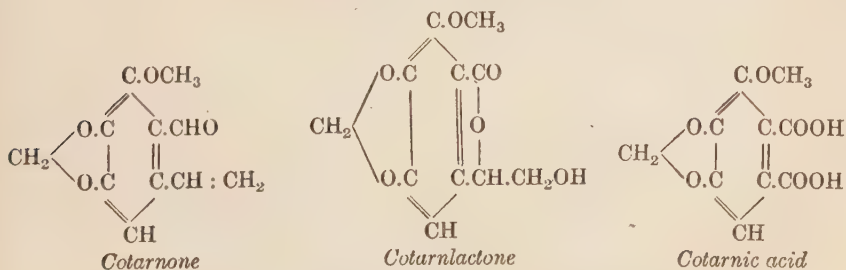
The formula for cotarnic acid has been confirmed by Perkin,

[1] *Annalen*, 1844, **50**, 19.
[2] Anderson, *ibid.* 1853, **86**, 187.
[3] *Ibid.* 1888, **249**, 141 ; 1889, **254**, 341.

Robinson and Thomas's synthesis of this acid [1] from 5 : 6-methylene-dioxy-1-hydrindone (I) as a starting-point. This was nitrated, the nitro-group reduced, replaced by hydroxyl, and the latter methylated. The 7-methoxy-5 : 6-methylenedioxy-1-hydrindone so produced was condensed with piperonal, and the product (II) oxidised with permanganate when it yielded cotarnic acid (*see* p. 281).
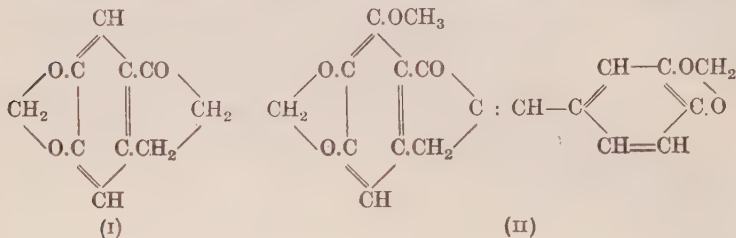
The formation of cotarnone from cotarninemethinemethiodide by the action of potash, led Roser to represent cotarnine and its salts by the following formulæ,[2] the loss of a molecule of water in the formation of cotarnine salts being explained by the production of a reduced pyridine ring :

Cotarnine (Roser)   *Cotarnine hydrochloride* (Roser)
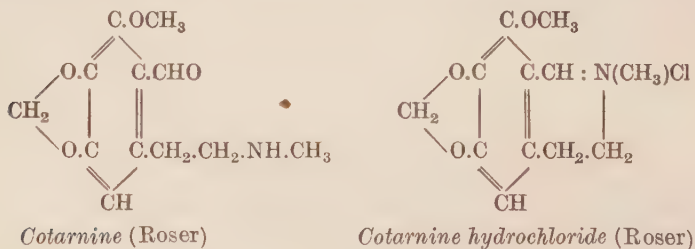
The positions of the methoxyl and dioxymethylene groups left unsettled by Roser were determined by Freund and Becker,[3] and their results were confirmed by the synthesis of cotarnic acid described above. Decker pointed out [4] that it was improbable that a secondary amine group and the aldehyde group — CHO could co-exist in the same molecule, and suggested that the reactions of cotarnine could be better accounted for by a bicyclic formula. Hantzsch and Kalb,[5] showed that the electrical conductivities of solutions of cotarnine indicated the existence in such solutions of an

[1] *Trans. Chem. Soc.* 1909, **95,** 1977.
[2] *Annalen,* 1889, **254,** 334, 359 ; 1893, **272,** 221.
[3] *Berichte,* 1903, **36,** 1521.
[4] *Journ. prakt. Chem.* 1893 [ii], **47,** 222.
[5] *Berichte,* 1899, **32,** 3109.

equilibrium mixture of two or possibly three forms,[1] one having Roser's formula, another Decker's formula, and a third having the formula of the ammonium base (*see below*) corresponding to that used by Roser for cotarnine salts. Dobbie, Lauder and Tinkler,[2] by comparison of the ultra-violet spectra of solutions of cotarnine, found that the solid alkaloid probably possesses the constitution assigned to it by Decker, whilst in solution in dissociating solvents such as water or alcohol, it possesses, at least in part, the constitution assigned by Roser [3] to the salts.

$$C.OCH_3$$

$$CH_2 \begin{cases} O.C & C.CHOH.N.CH_3 \\ O.C & C.CH_2 \!-\! CH_2 \end{cases}$$
$$CH$$
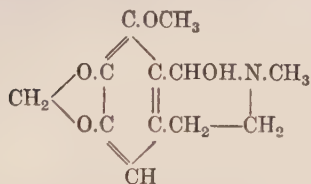
Cotarnine (Decker)
ψ-*Cotarnine* (Hantzsch and Kalb)

$$C.OCH_3$$

$$CH_2 \begin{cases} O.C & C.CH : N(CH_3).OH \\ O.C & C.CH_2.CH_2 \end{cases}$$
$$CH$$
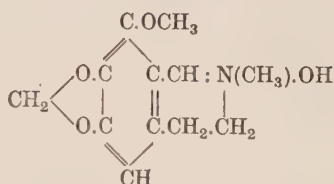
Cotarnine in dissociating solvents

In assigning a formula to hydrocotarnine the chief point to be accounted for is the ready oxidation of this tertiary base to the secondary amine cotarnine. Roser assumed that in this reaction a partially reduced pyridine ring is opened, giving rise to the side-chain of cotarnine, thus :

$$CH_3O.C \quad CH_2 \quad H_2O$$
$$CH_2 \begin{cases} O.C & C & N.CH_3 \\ O.C & C & CH_2 \end{cases}$$
$$CH \quad CH_2$$

Hydrocotarnine (Roser)

$$CH_3O.C \quad CH_2OH$$
$$CH_2 \begin{cases} O.C & C & NHCH_3 \\ O.C & C & CH_2 \end{cases}$$
$$CH \quad CH_2$$

Intermediate product

$$CH_3O.C \quad CHO$$
$$CH_2 \begin{cases} O.C & C & NHCH \\ O.C & C & CH_2 \end{cases}$$
$$CH \quad CH_2$$
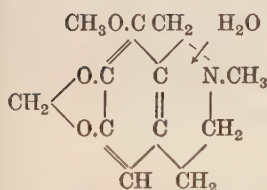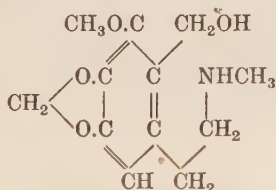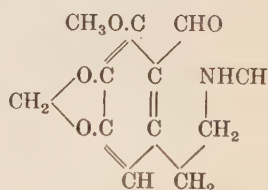
Cotarnine (Roser)

Utilising the formulæ assigned to the two products of hydrolysis of narcotine, viz., hydrocotarnine and opianic acid, Roser constructed the formula for narcotine [4] shown on the top of p. 284, which has been confirmed by Perkin and Robinson's synthesis of narcotine from meconin and cotarnine.[5]

A synthesis of narcotine was attempted by Liebermann,[6] who, by

[1] *Cf.* Freund and Bamberg, *Berichte*, 1902, **35**, 1739.
[2] *Trans. Chem. Soc.* 1903, **83**, 598.
[3] *Loc. cit.*
[4] *Annalen*, 1888, **249**, 156 ; 1889, **254**, 334, 351 ; 1893, **272**, 221.
[5] *Trans. Chem. Soc.* 1911, **99**, 775.
[6] *Berichte*, 1896, **29**, 180 ; 1904, **37**, 211.

$$\text{Narcotine structure}$$
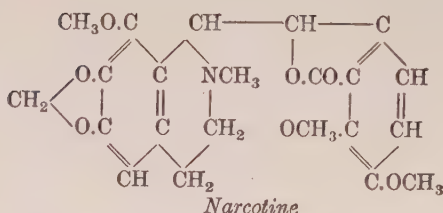
Narcotine

condensing opianic acid and hydrocotarnine, obtained *iso*narcotine, distinguished from narcotine by its melting-point, 194°, instead of 176°, and by the fact that it gives a red instead of a green coloration with sulphuric acid.

The synthesis of meconin by Fritsch has been referred to already (p. 280). Cotarnine has been synthesised by Salway [1] from myristicin (i) as a starting-point. This was transformed into β-3-methoxy-4 : 5 methylenedioxyphenylpropionic acid (ii), the amide of which was converted by Hofmann's reaction into β-3-methoxy-4 : 5-methylenedioxyphenylethylamine, and the phenylacetyl derivative (iii) of this was then condensed by heating it in xylene solution with phosphoric oxide, giving rise to the two possible dihydro*iso*quinoline derivatives. The first (iv) of these substances, 8-methoxy-6 : 7-methylenedioxy-1-benzyl-3 : 4-dihydro*iso*quinoline, on conversion into the methochloride and reduction with tin and hydrochloric acid, gave 1-benzylhydrocotarnine, and this on oxidation with manganese dioxide and sulphuric acid yielded cotarnine (vi). The isomeride (v) on like treatment furnished an isomeride, which was named *neo*cotarnine (vii), colourless prisms, m.p. 124° (*decomp.*).

$$\text{(i)} \qquad \text{(ii)}$$

$$\text{(iii)}$$
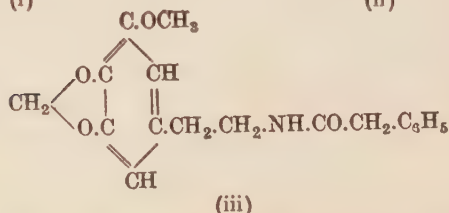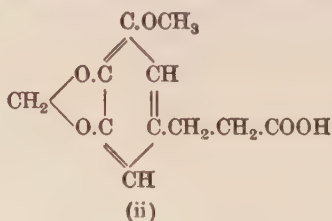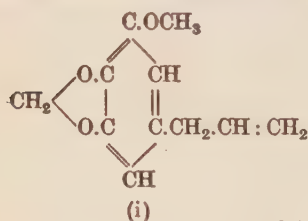
[1] *Trans. Chem. Soc.* 1910, **97**, 1208. *Cf.* Decker and Becker, *Annalen*, 1913, **395**, 328.

$CH_3O.C \quad C.CH_2.C_6H_5$

$.O.C \quad C \quad N$

$CH_2<$

$.O.C \quad C \quad CH_2$

$CH \quad CH_2$

(iv)

$C.OCH_3$

$.O.C \quad CH$

$CH_2<$

$.O.C \quad C$

$C \quad CH_2$

$C_6H_5.CH_2.C \quad CH_2$

N

(v)

$C.OCH_3$

$.O.C \quad C.CHO$

$CH_2<$

$.O.C \quad C.CH_2.CH_2.NH.CH_3$

CH

(vi)

Cotarnine

$C.OCH_3$

$.O.C \quad CH$

$CH_2<$

$.O.C \quad C.CH_2.CH_2.NH.CH_3$

$C.CHO$
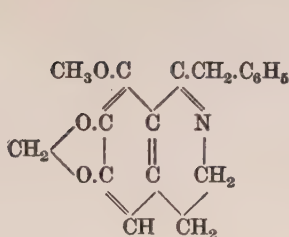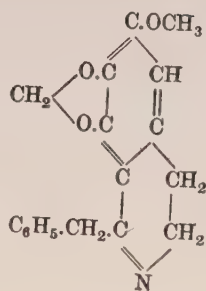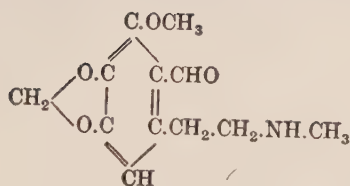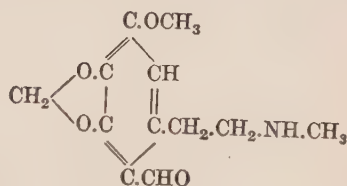
(vii)

neo*Cotarnine*

The syntheses of meconin and cotarnine having been effected, Perkin and Robinson completed this work by condensing these two substances in presence of potassium carbonate or by simply boiling them together in alcoholic solution.[1] The product obtained proved to be the alkaloid GNOSCOPINE, an inactive isomeride of narcotine obtained from opium by T. and H. Smith,[2] who also showed that this substance is formed when narcotine is boiled in acetic acid solution, and that it gives the same colour reactions as narcotine, and, like this alkaloid, is oxidised to opianic acid and cotarnine. These observations were extended by Rabe and MacMillan,[3] who found that when narcotine is boiled in dilute acetic acid it is racemised to gnoscopine, and the latter partly decomposed into nornarceine (see p. 288), cotarnine and meconin. Perkin and Robinson deracemised their synthetic gnoscopine and also natural gnoscopine by crystallisation of the *d-* and *l-*bromocamphorsulphonates. The three isomerides thus obtained had the following characters:

dl-*Narcotine* (*gnoscopine*), colourless needles, m.p. 229°; picrate, yellow prisms, m.p. 188°–189°; methiodide, $B.CH_3I.2H_2O$, magnificent prisms, m.p. 210°–212° (*dry*).

[1] *Trans. Chem. Soc.* 1911, **99**, 775.
[2] *Pharm. Journ.* 1878 [iii], **9**, 82; 1893 [iii], **23**, 794.
[3] *Berichte*, 1907, **40**, 3280; *Annalen*, 1910, **377**, 223.

d-*Narcotine.* Colourless needles, m.p. 175°, $[\alpha]_D + 199 \cdot 92°$ in chloroform.

l-*Narcotine* (natural narcotine). Colourless needles, m.p. 175°, $[\alpha]_D - 199 \cdot 85°$ in chloroform.

The relationship of narcotine to Liebermann's *iso*narcotine obtained by condensing hydrocotarnine with opianic acid is shown by the following formulæ : [1]

Narcotine   iso*Narcotine*
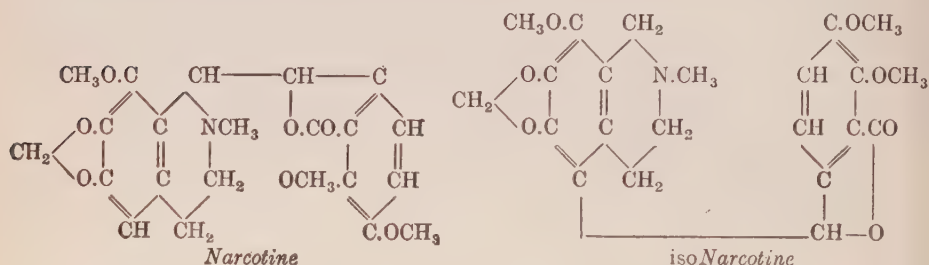
Hope and Robinson [2] found subsequently that nitro- and monohalogenated meconins condensed even more readily than meconin itself with cotarnine to yield the corresponding substituted gnoscopines, but whilst iodomeconin yielded in this way the iodo-derivative of natural gnoscopine (α-gnoscopine), nitromeconin furnished the nitro-derivative of an isomeric base β-gnoscopine, which is a stereoisomeride of the α-form yielding the same oxidation products and being convertible into narceine. So far β-gnoscopine has not been resolved into optically active forms, but it can be partially converted into α-gnoscopine by long heating in aqueous ethyl alcohol solution in sealed tubes at 100° C.

Narceine, $C_{23}H_{27}O_8N \cdot 3H_2O$. This alkaloid was obtained by Pelletier in 1832, and was subsequently characterised by Courbe and by Anderson.[3] The latter assigned to it the formula, $C_{23}H_{29}O_9N$, which was confirmed by Beckett and Wright and by Claus and Meixner. Freund,[4] however, observed that the base crystallised with three molecules of water, of which only two are lost at 100° ; consequently the composition of the substance examined by former workers was $C_{23}H_{27}O_8N \cdot H_2O$.

Narceine remains dissolved in opium extract after the removal

[1] Perkin and Robinson, *Trans. Chem. Soc.* 1911, **99**, 775; and Jones, Perkin and Robinson, *Trans. Chem. Soc.* 1912, **101**, 258.

[2] *Trans. Chem. Soc.* 1911, **99**, 1153, 2114 ; 1914, **105**, 2085. *Cf.* 1913, **103**, 361 ; 1914, **105**, 1456.

[3] *Annalen*, 1853, **86**, 182.

[4] *Ibid.* 1893, **277**, 20.

of morphine and codeine (p. 258) and the precipitation of narcotine, thebaine and papaverine from the mother liquor by dilution and addition of ammonia ; it is isolated by decolorising this brown liquid by lead acetate and removing the excess of lead by sulphuretted hydrogen. The filtrate is made alkaline with ammonia and exposed in a warm place, when narceine gradually crystallises out, and may be recrystallised from alcohol by addition of water. It forms slender needles or prisms, m.p. $170°$ or $140°–145°$ (*dry*), $[\alpha]_D\ 0°$, slightly soluble in cold 80 per cent. alcohol (1 in 945 at $13°$) or water (1 in 1,285 at $13°$), but much more soluble when warmed. It dissolves in alkaline liquids, including ammonia, forming metallic derivatives, which crystallise from alcohol on addition of ether with 1 mol. of the solvent, the general formula being $C_{23}H_{26}O_8N.M.C_2H_5OH$, where M represents a monovalent metal.

Narceine behaves as a feeble monoacidic tertiary base and yields well-crystallised salts. The hydrochloride, $B.HCl$, crystallises out when the alkaloid is dissolved in aqueous hydrochloric acid, and separates with $5\tfrac{1}{2}H_2O$ in the cold, or with $3H_2O$ from hot solutions. If a methyl alcohol solution of hydrogen chloride is used the salt crystallises with 1 mol. of methyl alcohol, $B.HCl.CH_3OH$. The sulphate, $B.H_2SO_4.2H_2O$, forms slender needles.

Narceine gives a characteristic blood-red colour with chlorine water followed by addition of ammonia. Weak iodine solution colours narceine blue. It dissolves in sulphuric acid with a brown colour, becoming blood-red on warming.

The alkaloid has been prepared [1] by heating narcotinemethochloride with caustic soda, when sodium chloride and narceine result according to the following equation :

$$C_{22}H_{23}O_7N.CH_3Cl + NaHO = C_{23}H_{27}O_8N + NaCl$$
$$\textit{Narcotinemethochloride} \qquad\qquad \textit{Narceine}$$

Homonarceine, $C_{24}H_{29}O_3N.3H_2O$, is similarly made from narcotinethochloride.

Narceine contains three methoxyl groups, reacts with phenylhydrazine and hydroxylamine, furnishing a phenylhydrazone and an oxime, and esterifies with alcohols in presence of hydrogen chloride. From a study of these reactions, and in particular the partial synthesis of narceine from narcotine, Freund and Frankforter [1] represented the alkaloid as related to narcotine in the following way, and

[1] Freund and Frankforter, *Annalen*, 1893, **277**, 31. *Cf.* Roser, *ibid.* 1888, **247**, 167, and for a better method *see* Hope and Robinson, *Trans. Chem. Soc.* 1914, **105**, 2085.

this has been confirmed by Freund and Oppenheimer's [1] observation that narceine yields an oximino derivative, which on exhaustive methylation gives trimethylamine, hemipinic acid (3 : 4-dimethoxy-phthalic acid) and 2-cyano-3-methoxyl-4 : 5-methylenedioxy-1-vinyl-benzene (cotarnonitrile) a substance first obtained by Roser from cotarnine.[2]
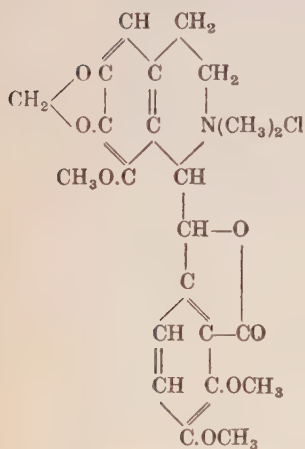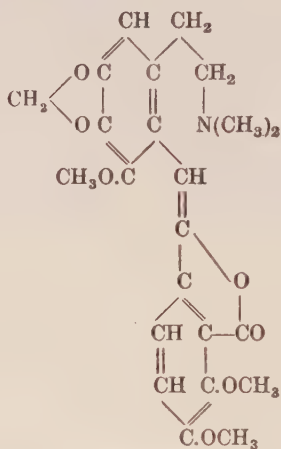
Narcotinemethochloride   *Intermediate product*   *Narceine*
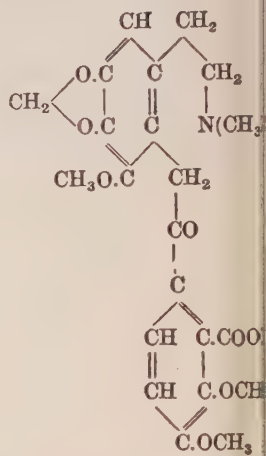
It has been pointed out already that on heating in acetic acid solution, *l*-narcotine yields *dl*-narcotine (gnoscopine), and some nornarceine, $C_{22}H_{25}O_8N.3H_2O$ (felted needles, decomposing at 205°–222°). This latter change takes place in the following way, and is analogous with that of cinchonine into cinchonicine [3] (p. 156).
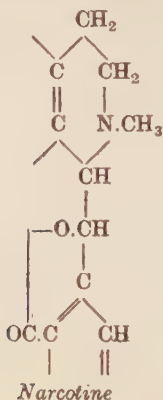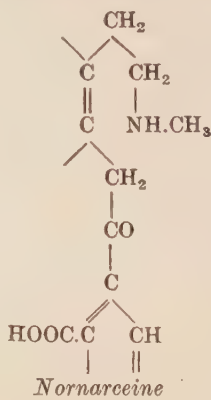
Narcotine   *Nornarceine*

[1] *Berichte*, 1909, **42**, 1084.
[2] *Annalen*, 1889, **254**, 338.
[3] *Berichte*, 1907, **40**, 3280.

Oxynarcotine, $C_{22}H_{23}O_8N$. This alkaloid, which occurs in opium in minute quantities, was separated by Beckett and Wright [1] from impure narceine. It crystallises from hot alcohol in small needles. Its close relationship to narcotine is shown by the formation from it of cotarnine, $C_{12}H_{15}O_4N$, and hemipinic acid, $C_{10}H_{10}O_6$, when it is oxidised by ferric chloride ; narcotine under these circumstances furnishing cotarnine and opianic acid, $C_{10}H_{10}O_5$. It is doubtful whether oxynarcotine is a chemical individual.

Papaverine, $C_{20}H_{21}O_4N$. This alkaloid was first obtained by Merck [2] in 1848. It occurs in the mixture of bases precipitated by ammonia from the mother liquors of opium extract from which morphine and codeine hydrochlorides have been crystallised, from which it is separated together with some narcotine by hot alcohol. The alkaloid is finally purified by conversion into the acid oxalate, $B.H_2C_2O_4$, m.p. 199°, which is nearly insoluble in alcohol, that of narcotine being soluble. The base is regenerated by the addition of calcium chloride to the aqueous solution of the salt and precipitation from the filtrate with ammonia solution.

Papaverine crystallises in rhombic prisms or needles, m.p. 147°, $[\alpha]_D$ 0°, is insoluble in water, soluble in hot alcohol or chloroform, and slightly so in cold alcohol or ether. It behaves as a monoacidic base and forms salts with acids, but, since the base exerts only a mild soporific action, none of these are employed in medicine. The hydrochloride, $B.HCl$, forms monoclinic plates, m.p. 231°, sparingly soluble in water (1 in 37 at 18°).

The colour reactions ascribed to papaverine are often due to cryptopine,[3] but this apparently does not apply to the following test which is given by synthetic papaverine. With pure cold sulphuric acid it dissolves to a colourless solution, which becomes rose-red at 110°, darkening to violet at 200°, the colour being discharged on adding water. According to Warren,[3] Marquis's reagent gives with papaverine ferricyanide a blue colour, changing to violet, green and brown.

Constitution. Information regarding the structure of papaverine

[1] *Journ. Chem. Soc.* 1876, **29,** 461. *Cf.* Gadamer and Bruck, *Arch. Pharm.* 1923, **261,** 117.

[2] *Annalen,* 1848, **66,** 125 ; 1849, **72,** 50.

[3] Pictet and Kramers, *Berichte,* 1910, **43,** 1329. *Cf.* Hesse, *J. prakt. Chim.* 1903 [ii], **68,** 190 ; Pyman and Reynolds, 1910, **97,** 1323 (footnote) ; Warren, *Journ. Amer. Chem. Soc.* 1915, **37,** 2402 ; Reichard, *Pharm. Centr.-h.* 1907, **48,** 288.

is principally due to the work of Goldschmiedt and collaborators.[1] It behaves as a tertiary amine and gives a methiodide, $B.CH_3I.4H_2O$ m.p. 195° (*dry*) ; the corresponding methohydroxide obtained by the action of alkali is crystalline and markedly alkaline in reaction. On treatment with hydriodic acid and red phosphorus the alkaloid furnishes four molecular proportions of methyl iodide and yields papaveroline, $C_{16}H_9(OH)_4N$.

The relationship of the principal substances formed by the oxidation of the alkaloid is shown in the following scheme :

<div align="center">

Papaverine, $C_{20}H_{21}O_4N$

</div>

Oxidation by cold permanganate	*Oxidation by hot permanganate*
Papaveraldine, $C_{20}H_{19}O_5N$	Papaverinic acid, $C_{16}H_{13}O_7N$
Dimethoxy*iso*quinolinecarb-oxylic acid	Veratric acid, *meta*hemipinic acid and pyridine-2 : 3 : 4-tricarb-oxylic acid
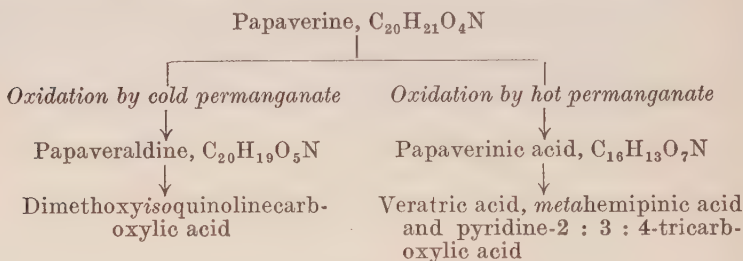
Papaveraldine, $C_{20}H_{19}O_5N$. This substance, the principal product of the action of cold acid permanganate on papaverine, forms colourless scales, m.p. 210°, yields well-crystallised yellow salts, which are dissociated in water, and reacts as a tertiary base. It contains four methoxyl groups, and with hydroxylamine forms an oxime existing in two stereoisomeric forms. Miss Dobson and Professor W. H. Perkin have shown that the alkaloid, XANTHALINE, isolated from opium by T. and H. Smith,[2] is identical with papaveraldine.[3] On reduction with zinc dust in acetic acid, papaveraldine yields the secondary alcohol, papaverinol.[4] When fused with potash it undergoes hydrolysis, furnishing veratric acid (4 : 5-dimethoxy-phthalic acid) and a dimethoxy*iso*quinoline, which is converted into cinchomeronic and *meta*hemipinic acids by oxidation with acid permanganate and must, therefore, have the two methoxy groups in positions 6 and 7.

<div align="center">

$C_{20}H_{19}O_5N + H_2O = C_6H_3.COOH.(OCH_3)_2 + C_9H_5(OCH_3)_2N$
Papaveraldine   *Veratric acid*   *Dimethoxy*iso-quinoline

</div>

[1] *Monats.* 1883, **4**, 704 : 1885, **6**, 372, 667, 956 ; 1886, **7**, 488 ; 1887, **8**, 510 ; 1888, **9**, 42, 327, 349, 679, 762, 778 ; 1889, **10**, 673, 692 ; 1898, **19**, 324.

[2] *Pharm. Journ.* 1893 [iii], **52**, 793.

[3] *Trans. Chem. Soc.* 1911, **99**, 135 ; and Mason and Perkin, *ibid.* 1914, **105**, 2013.

[4] Stuchlik, *Monats.* 1900, **21**, 813.

$$
\begin{array}{c}
\text{CH} \\
\text{N} \quad \text{C.COOH} \\
\text{CH} \quad \text{C.COOH} \\
\text{CH}
\end{array}
\quad \longleftarrow \quad
\begin{array}{c}
\text{CH} \quad \text{CH} \\
\text{N} \quad \text{C} \quad \text{C.OCH}_3 \\
\text{CH} \quad \text{C} \quad \text{C.OCH}_3 \\
\text{CH} \quad \text{CH}
\end{array}
\quad \longrightarrow \quad
\begin{array}{c}
\text{CH} \\
\text{COOH.C} \quad \text{C.OCH}_3 \\
\text{COOH.C} \quad \text{C.OCH}_3 \\
\text{CH}
\end{array}
$$
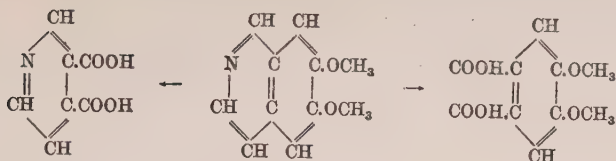
Cinchomeronic acid   *Dimethoxyisoquinoline*   meta*Hemipinic acid*

The position in which the veratryl residue is attached to the *iso*quinoline nucleus in papaveraldine and papaverine is determined by the formation of pyridine-2 : 3 : 4-tricarboxylic acid in the oxidation of papaverine by hot permanganate.

On the basis of these results, Goldschmiedt assigned the following formula to papaveraldine :

$$
\begin{array}{c}
\text{C---CO---C} \quad \text{CH} \\
\text{CH} \quad \text{CH} \quad \text{N} \quad \text{C} \quad \text{C.OCH}_3 \\
\text{OCH}_3.\text{C} \quad \text{CH} \quad \text{CH} \quad \text{C} \quad \text{C.OCH}_3 \\
\text{C.OCH}_3 \quad \text{CH} \quad \text{CH}
\end{array}
\qquad
\begin{array}{c}
\text{C.COOH} \\
\text{N} \quad \text{C.COOH} \\
\text{CH} \quad \text{C.COOH} \\
\text{CH}
\end{array}
$$
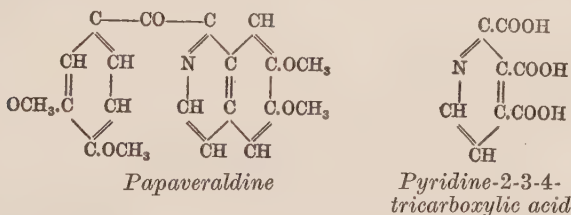
Papaveraldine   *Pyridine-2-3-4-*
tricarboxylic acid

Papaverinic acid, $C_{16}H_{13}O_7N \cdot H_2O$, crystallises in small tablets, m.p. 233°. It is dibasic, readily forms an anhydride, furnishes an oxime and a phenylhydrazone, contains two methoxyl groups,[1] and on oxidation yields veratric, metahemipinic and pyridine-2 : 3 : 4-tricarboxylic acids, and hence is represented as 1-veratroylcinchomeronic acid.[1]

The constitution of papaverine follows from that of papaveraldine, from which it differs in composition by the substitution of — CH_2 — for — CO — .[2]

$$
\begin{array}{c}
\text{C}-------\text{CH}_2-------\text{C} \quad \text{CH} \\
\text{CH} \quad \text{CH} \quad \text{N} \quad \text{C} \quad \text{C.OCH}_3 \\
\text{CH}_3\text{O.C} \quad \text{CH} \quad \text{CH} \quad \text{C} \quad \text{C.OCH}_3 \\
\text{C.OCH}_3 \quad \text{CH} \quad \text{CH}
\end{array}
$$
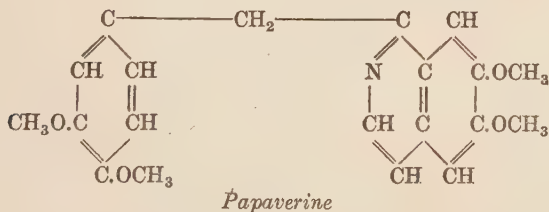
Papaverine

The first attempt to synthesise papaverine was made by Fritsch [3]

[1] *Cf.* Goldschmiedt and Hönigschmid, *Monats.* 1903, **24**, 681.
[2] Goldschmiedt, *ibid.*, 1888, **9**, 778. *Cf.* Königs, *Berichte*, 1899, **32**, 3612.
[3] *Annalen*, 1903, **329**, 37.

by condensing $3 : 4 : 3' : 4'$-tetramethoxydeoxybenzoin with acetal-amine, which furnished an isomeride melting at a higher temperature than papaverine.

A complete synthesis was effected by Pictet and Gams,[1] who treated veratrole (o-dimethoxybenzene) with acetyl chloride and aluminium chloride, thus producing acetoveratrone ($4 : 5$-dimethoxy-acetophenone), the oximino derivative of which was reduced and the resulting aminoacetoveratrone, $C_6H_3(OCH_3)_2.CO.CH_2.NH_2$, condensed with homoveratroyl chloride ($4 : 5$-dimethoxyphenyl-acetyl chloride), $C_6H_3(OCH_3)_2.CH_2.COCl$, yielding homoveratroyl-aminoacetoveratrone, $C_6H_3(OCH_3)_2 . CO . CH_2 . NH . CO.CH_2.C_6H_3$ $(OCH_3)_2$. This on reduction gave homoveratroylhydroxyveratryl-amine, $C_6H_3(OCH_3)_2 . CHOH . CH_2 . NH . CO . CH_2 . C_6H_3(OCH_3)_2$, which when boiled with phosphoric acid in xylene solution lost 2 mols. of water and yielded papaverine ($6 : 7$-dimethoxy-1-veratryl-

isoquinoline), $\overline{C_6H_2(OCH_3)_2.CH : CH.N : C.CH_2.C_6H_3(OCH_3)_2}$.
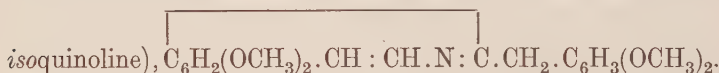
The reduction products of papaverine are of some interest, in view of their relationship to other alkaloids of this series. Gold-schmiedt stated that papaverine, on reduction by tin and hydrochloric acid, yielded tetrahydropapaverine, m.p. $200°$–$201°$, together with an amorphous base.[2] Freund and Beck by electrolytic reduction of papaveraldine obtained an amorphous isotetrahydropapaverine yielding a crystalline hydriodide.[3] On reinvestigating these pro-ducts, Pyman [4] found that Goldschmiedt's amorphous base was identical with Freund and Beck's isotetrahydropapaverine and that the product was a true tetrahydropapaverine (formula I). Gold-
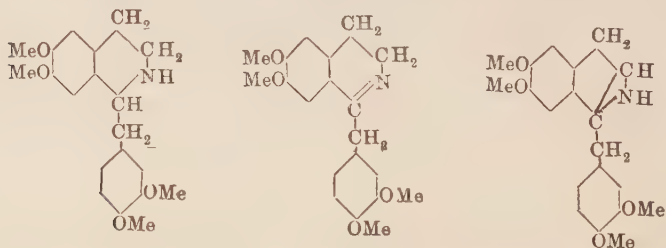
I *Tetrahydropapaverine*　　II $3 : 4$-*Dihydropapaverine*　　III *Pavine*

[1] *Compt. rend.* 1909, **149**, 210.
[2] *Monats.* 1886, **7**, 485 ; 1898, **19**, 324.
[3] *Berichte*, 1904, **37**, 3321.
[4] *Trans. Chem. Soc.* 1909, **95**, 1610 ; 1915, **107**, 176. *Cf.* Pyman and Reynolds, *ibid.* 1910, **97**, 1320.

schmiedt's supposed tetrahydropapaverine, however, proved to have the composition of a dihydropapaverine, $C_{20}H_{23}O_4N$ (not identical with Pictet and Finkelstein's [1] 3 : 4-dihydropapaverine (formula II)), which Pyman named PAVINE, and to which he eventually assigned formula III on the grounds that (1) since it behaves as a secondary base one hydrogen must be attached to the nitrogen ; (2) as it is stable to oxidising and reducing agents the reduced pyridine ring cannot contain a double bond ; and (3) the nature of the products formed when the base is degraded by Hofmann's method.

Tetrahydropapaverine in presence of hydrochloric acid condenses with acetal to form two stereoisomeric bases, which are structural isomerides of corydaline and have been named α- and β-CORALYDINES ; the former, the chief product of the reaction, has m.p. 148°, whilst the β-form melts at 115°.   When the condensation takes place with methylal only one base is formed, viz., norcoralydine, $C_{21}H_{25}O_4N$, which forms colourless leaflets, m.p. 157°–158°, and, like corydaline, slowly becomes yellow on exposure to air, and is oxidised by iodine solution to dehydronorcoralydine.[2]

Similarly, Schneider [3] and his collaborators have shown that sulphoacetic acid (acetic anhydride with concentrated sulphuric acid) converts papaverine into a yellow crystalline salt, $C_{24}H_{25}O_9NS$. H_2O, the quaternary ammonium base of which, on warming in water, changes into an isomeric ketonic base from which salts of the original base are regenerated on addition of acids, in which respect the latter, which is named CORALYNE (*hexadehydrocoralydine*), closely resembles berberine and dehydrocorydaline ; the ketonic base is named ψ-CORALYNE (*acetopapaverine*).   These two, like the two coralydines and norcoralydine, yield *m*-hemipinic acid on oxidation. On reduction coralyne yields dihydrocoralydine and some α-coralydine. To these bases the formulæ on the top of p. 294 have been assigned.

For conversion of papaverine into laudanosine, see p. 294 ; into laudanine, see p. 296 ; into glaucine, see p. 244.

Laudanosine, $C_{21}H_{27}O_4N$. This alkaloid occurs in the liquor from which thebaine is precipitated, and is isolated by the method already described (p. 258). The crude alkaloid is purified by

[1] *Compt. rend.* 1909, **148**, 925.
[2] Pictet (with Malinowski), *Berichte*, 1913, **46**, 2688 ; (with Chou) *ibid.* 1916, **49**, 370.   *Cf.* Späth and Lang, *ibid.* 1921, **54**, 3064.
[3] (With Schroeter) *ibid.* 1920, **53**, 1459; (with Böger) *ibid.* 1921, **54**, 2021 ; (with Köhler) *ibid.* 1921, **54**, 2031 ; (with Nitze) *ibid.* 1923, **56**, 1036 (deals with propionylpapaverine and homocoralyne).
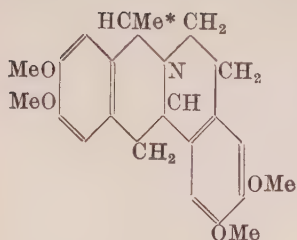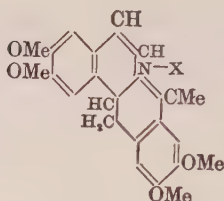
a- and β-Coralydines　　　Coralyne　　ψ-Coralyne
(* CH² in norcoralydine) (*Hexadehydrocoralydine*) (*Acetopapaverine*)
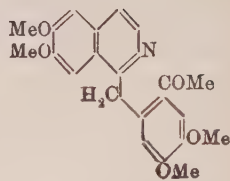
extracting with small quantities of ether, in which laudanosine is very soluble, and finally by precipitation with potassium iodide. The free alkaloid crystallises from hot benzene in needles, m.p. 89°, $[\alpha]_D^{15°} + 103 \cdot 23°$ in alcohol, is soluble in alcohol, chloroform, hot benzene, or ether (1 in 19·3 at 16°), but insoluble in water or alkalis. The solution in alcohol is alkaline, and the alkaloid and its salts are bitter. The hydriodide, $B \cdot HI \cdot \frac{1}{2}H_2O$, forms small prisms readily soluble in alcohol, sparingly so in water, and the acid oxalate, $B \cdot H_2C_2O_4 \cdot 3H_2O$, prisms easily soluble in water. Laudanosine is not coloured by ferric chloride, but with ferric oxide and sulphuric acid gives a brown colour, changing to green when warmed at 150°. With sulphuric acid alone it gives a rose-red coloration, changing to deep reddish-violet on warming to 150°.

Laudanosine contains four methoxyl groups. By exhaustive methylation it yields trimethylamine and laudanosen (tetramethoxy-*o*-vinylstilbene), $CH_2 : CH \cdot C_6H_2(OCH_3)_2 \cdot CH : CH \cdot C_6H_3(OCH_3)_2$.[1] On oxidation with manganese dioxide and sulphuric acid it yields veratraldehyde and 4 : 5-dimethoxy-2 : β-methylaminoethylbenzaldehyde.[2] The latter combines with acids to form salts of 6 : 7-dimethoxy-2-methyl-3 : 4-dihydro*iso*quinolinium hydroxide, thus behaving similarly to cotarnine (p. 281) and hydrastinine.

The constitution of laudanosine has been determined by Pictet and Athanasescu,[3] who have prepared it by reducing papaverine methochloride with tin and hydrochloric acid and deracemising the N-methyltetrahydropapaverine so obtained by fractional crystallisation of the quinate. Laudanosine must, therefore, be represented by the following formula :

[1] Decker and Galatty, *Berichte*, 1909, **42**, 1179.
[2] Pyman, *Trans. Chem. Soc.* 1909, **95**, 1267.
[3] *Berichte*, 1900, **33**, 2346. *Cf.* Pyman and Reynolds, *Trans. Chem. Soc.* 1910, **97**, 1323.

$$C\text{———}CH_2\text{———}CH\quad CH$$
$$CH\quad CH\qquad CH_3.N\quad C\quad C.OCH_3$$
$$CH_3O.C\quad CH\qquad CH_2\quad C\quad C.OCH_3$$
$$C.OCH_3\qquad CH_2\quad CH$$
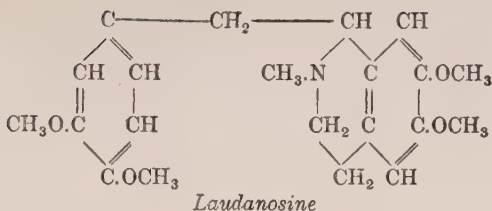
Laudanosine

Racemic laudanosine, so prepared, crystallises from light petroleum or dilute alcohol in needles, m.p. 115°. The platinichloride, m.p. 160°, and the picrate, m.p. 174°, are crystalline.

A complete synthesis of laudanosine has been effected by Pictet and Finkelstein [1] by a process similar to that used for papaverine (p. 292), viz., the condensation of homoveratrylamine (I) with homoveratroyl chloride (II), giving homoveratroylhomoveratrylamine, which with phosphoric oxide loses H_2O and yields 3 : 4-dihydropapaverine (III). This was converted into the methochloride and reduced to laudanosine (*see above*).

$$CH$$
$$CH_3O\ C\quad CH\quad NH_2\qquad\qquad COCl.CH_2.C$$
$$CH_3O.C\quad C\quad CH_2\qquad\qquad CH\quad CH$$
$$CH\quad CH_2\qquad\qquad\qquad CH\quad C.OCH_3$$
$$(I)\qquad\qquad\qquad\qquad C.OCH_3$$
$$(II)$$

$$CH\quad C\text{———}CH_2\text{———}C$$
$$CH_3O.C\quad C\quad N\qquad\qquad CH\quad CH$$
$$CH_3O\ C\quad C\quad CH_2\qquad CH\quad C.OCH_3$$
$$CH\quad CH_2\qquad\qquad C.OCH_3$$
$$(III)$$
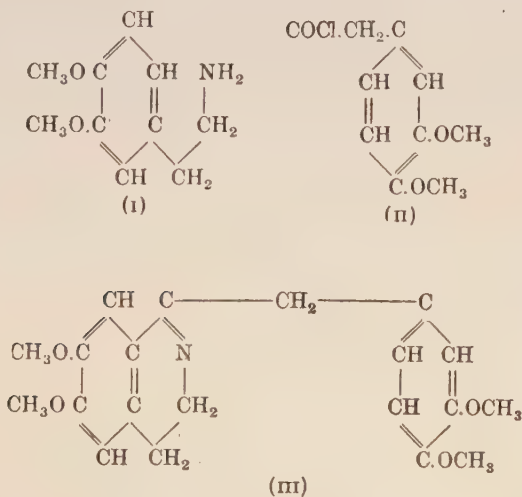
Laudanine, $C_{20}H_{25}O_4N$. The crude laudanine obtained as already described is purified by recrystallisation from dilute alcohol for the removal of small quantities of cryptopine, or it may be dissolved in acetic acid and the solution made alkaline

[1] *Compt. rend.* 1909, **148**, 925. For another synthesis *see* Gadamer, *Arch. Pharm.* 1911, **249**, 680.

with caustic soda when this impurity is precipitated, and the laudanine may then be isolated by addition of ammonium chloride. From laudanidine it is separated by repeated crystallisation of the hydrochloride.[1] It crystallises from dilute alcohol in tri-metric prisms, m.p. 166°, $[\alpha]_D$ 0°, is easily soluble in chloroform, benzene or hot alcohol, and dissolves in solutions of soda or potash, forming metallic derivatives, which are precipitated by excess of alkali ; it is nearly insoluble in ammonia solution. The hydriodide, $B.HI.H_2O$, is crystalline and sparingly soluble in water (1 in 500 at 15°).

With ferric chloride it gives a green coloration, and a deep red colour with ferric oxide and sulphuric acid.

The base contains three methoxyls and one hydroxyl group, and, according to Hesse,[2] yields a mixture of laudanine methiodide and r-laudanosine when treated with methyl iodide in methyl alcohol, so that r-laudanosine is the methyl ether of laudanine, an observation confirmed recently by Späth,[2] who has also shown that the hydroxyl group of laudanine is present in the benzyl residue, since on oxidation the ethylated base yields 4-methoxy-3-ethoxybenzoic acid (ethyl-*iso*vanillic acid), and similarly ethylcarbonatolaudanine is oxidised to ethylcarbonato*iso*vanillic acid. On these grounds Späth has assigned the formula given below to laudanine. In 1903, Pictet and Kramers [3] attempted a partial synthesis of laudanine by reducing trimethylpapaveroline methiodide, but this yielded an isomeric base *iso*LAUDANINE, m.p. 76°, which gave blue colorations with ferric chloride in sulphuric acid and with Fröhde's reagent. Similarly, Decker and Eichler [4] obtained ψ-LAUDANINE, m.p. 112°, picrate, m.p. 162°–163°, by reducing N-methylnorpapaverinium phenolbetaine with tin and hydrochloric acid.
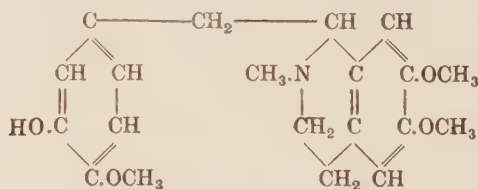
Laudanine (Späth)

[1] Hesse, *Annalen*, 1894, **282**, 209.

[2] *Journ. prakt. Chem.* 1902 [ii], **65**, 42. *Cf.* Späth, *Monats.* 1920, **41**, 297.

[3] *Arch. Sci. phys. nat.* 1903 [iv], **15**, 121.

[4] *Annalen*, 1913, **395**, 377. *Cf. ibid.* 1908, **358**, 288.
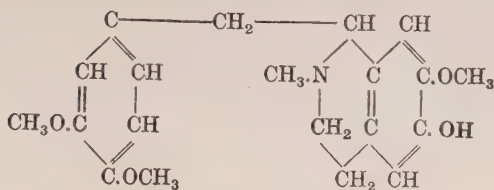
ψ-*Laudanine*

Späth and Lang[1] have synthesised laudanine by condensing homoveratrylamine with 3-ethylcarbonato-4-methoxyphenylpyruvic acid, dehydrating the resulting product with phosphoric oxide in toluene solution, converting the 1-ethylcarbonato*iso*vanillyl-6 : 7-dimethoxy-3 : 4-dihydro*iso*quinoline formed into the methiodide and then into the methochloride, which on reduction with tin and hydrochloric acid yielded a mixture of laudanine and ethylcarbonatolaudanine.

Laudanidine, $C_{20}H_{25}O_4N$. This alkaloid occurs associated with its isomeride laudanine,[2] from which it may be separated by repeated crystallisation of the hydrochlorides. Laudanidine closely resembles laudanine ; it melts at 177°, and has $[\alpha]_D - 87\cdot8°$ in chloroform. It is probably the lævo-form of laudanine.

Porphyroxine, $C_{19}H_{23}O_4N$. So long ago as 1837, Merck isolated from opium a product to which he gave this name, and which Hesse[3] subsequently found to be a mixture of alkaloids, including rhœadine and meconidine. A similar substance was obtained by Dey in 1882, both these preparations having the property of forming purple-coloured solutions with dilute acids, hence the name, a property it shares with rhœadine. Rakshit[4] has examined the material dissolved by ether from an extract obtained by triturating a mixture of Indian opium and lime with water, and has isolated from it a substance of the formula given above for which he proposes to retain the name porphyroxine. It is described as crystallising from light petroleum in pale yellow or colourless transparent prisms, m.p. 134°–135°, $[\alpha]_D - 139\cdot9°$ in chloroform, soluble in water, dilute acids, acetone, chloroform, and moderately so in alcohol, benzene, or ethyl acetate, sparingly in ether, or light petroleum, and almost insoluble in lime water or alkalis. Solutions in dilute acids become red on exposure to air. The alkaloid gives a red colour with sul-

[1] *Monats.* 1921, **42**, 273.
[2] Hesse, *Annalen*, 1894, **282**, 209.
[3] *Annalen, Suppl.* 1864–65, **4**, 50 ; 1870, **153**, 47.
[4] *Trans. Chem. Soc.* 1919, **115**, 455.

phuric acid. The salts are mostly crystalline, $B.HCl$, m.p. 155°, prismatic needles, nitrate, $B.HNO_3$, m.p. 122°, feathery tablets, the platinichloride, m.p. 204° (*decomp.*), picrate, $B.C_6H_3O_7N_3$, m.p. 198°, are crystalline powders.

Cryptopine, $C_{21}H_{23}O_5N$. This base was obtained in the form of its acid oxalate from thebaine residues by J. Smiles in Messrs. T. and H. Smith's laboratories [1] (*cf.* p. 266). According to Pictet and Kramers [2] commercial papaverine frequently contains up to 4 per cent. of cryptopine, and to this are due some of the colour reactions usually ascribed to papaverine and possibly to other alkaloids of opium.

It crystallises from alcohol in prisms, m.p. 218°, $[\alpha]_D$ 0°, is soluble in boiling alcohol (1 in 80), but sparingly soluble in cold alcohol, ether or benzene. The salts separate as jellies, but can usually be crystallised by warming the liquid : the oxalate, $B.H_2C_2O_4.4H_2O$, is the most characteristic salt. The aurichloride forms brownish-yellow needles, m.p. 205° (*decomp.*), and the platinichloride concentrically arranged needles, m.p. 204° (*decomp.*). With sulphuric acid it gives a violet colour, changing to green on warming to 150°.

The investigations of Pictet and Kramers [2] and of Danckwortt[3] indicated that cryptopine was a saturated base, contained an : NCH_3 group, two methoxyl groups, but no hydroxyl or carbonyl groups. No direct evidence of the presence of a dioxymethylene group was obtained, but since the alkaloid gave Gaebel's [4] reaction and a green coloration with sulphuric and gallic acids,[5] it was assumed that such a group was present and that the fifth oxygen must occur joined to two carbon atoms. In 1891, Rainy Brown and Perkin,[6] in a preliminary note, showed that the alkaloid yielded *m*-hemipinic acid on oxidation with permanganate, and up to 1916 this remained virtually the only observation bearing on the nuclear structure of the alkaloid. In the latter year, W. H. Perkin began the publication of the results of a long and ingenious investigation of this rare alkaloid.[7] In the

[1] *Pharm. Journ.* [ii], **8**, 595. *Cf.* Cook, *ibid.* p. 716 ; and Hesse, *Annalen, Suppl.* **8**, 310 ; 1874, **176**, 200.

[2] *Berichte*, 1910, **43**, 132.

[3] *Arch. Pharm.* 1912, **250**, 590.

[4] *Arch. Pharm.* 1910, **248**, 225.

[5] Labat, *Bull. Soc. chim.* 1909 [iv], **5**, 745.

[6] *Proc. Chem. Soc.* 1891, **7**, 166.

[7] *Trans. Chem. Soc.* 1916, **109**, 815–1028 ; 1919, **115**, 713–790. It has become customary to call cryptopine a rare alkaloid, but, according to Dr. H. E. Watt, Indian opium contains 0·3 per cent. (*Pharm. Journ.* 1918 [iv], **46**, 147).

first paper it is shown that after numerous attempts to obtain evidence of the presence of a piperonyl ring by hydrolytic and oxidation experiments the difficulty was solved by converting cryptopine into the methosulphate, $C_{21}H_{23}O_5N.Me_2SO_4$, reducing this in acid solution with sodium amalgam to tetrahydromethyl-cryptopine, $C_{22}H_{29}O_5N$, m.p. 107°, from which acetyl chloride eliminates water yielding anhydrotetrahydromethylcryptopine, $C_{22}H_{27}O_4N$, m.p. 107°. This substance on oxidation with dry potassium permanganate in acetone yielded four products:

(A) 4 : 5-Dimethoxy-2-β-dimethylaminoethylbenzaldehyde,
    $(CH_3O)_2.C_6H_2(CHO).CH_2.CH_2.NMe_2$.

(B) 5 : 6-Methylenedioxy-o-tolualdehyde, $CH_2:O_2:C_6H_2Me.CHO$.

(C) N-formyl-4 : 5-dimethoxy-2-β-methylaminoethylbenzoic acid,
    $(CH_3O)_2.C_6H_2(COOH).CH_2.CH_2.NMe.CHO$.

(D) 5 : 6-Methylenedioxy-o-toluic acid.

The formation of A and C indicates that cryptopine must have in its structure the grouping I, whilst the production of B and D shows that the alkaloid must also contain the piperonyl ring in the form of grouping II, and from these the structure of anhydrotetrahydro-methylcryptopine is represented by formula III:

I

III *Anhydrotetrahydromethylcryptopine*

II

IV *Tetrahydromethylcryptopine*
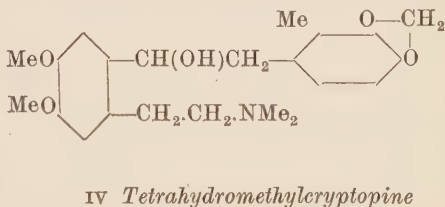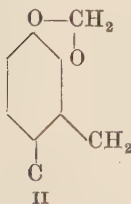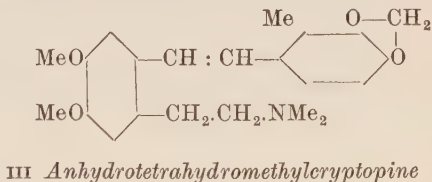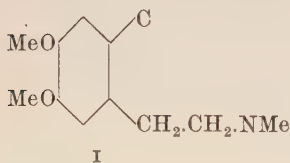
and, as this is formed from tetrahydromethylcryptopine by loss of water, the formula IV of the latter is obtained by the addition of the elements of water at the ethylene linkage, and evidence is produced that this change takes place as shown.[1]

[1] *Loc. cit.* p. 839.

Confirmatory evidence up to this point was obtained by treating anhydrotetrahydromethylcryptopine methosulphate with methyl alcoholic potassium hydroxide, which furnished trimethylamine and a non-nitrogenous substance, cryptopidene, $C_{20}H_{20}O_4$, m.p. 124°, which on oxidation with permanganate yields 5 : 6-methylenedioxy-o-tolualdehyde I (and the corresponding acid) as well as 4 : 5-di-methoxyvinylbenzaldehyde II (with m-opianic and m-hemipinic acids), from which the formula of cryptopidene is built up as follows :

I   II   III *Cryptopidene*
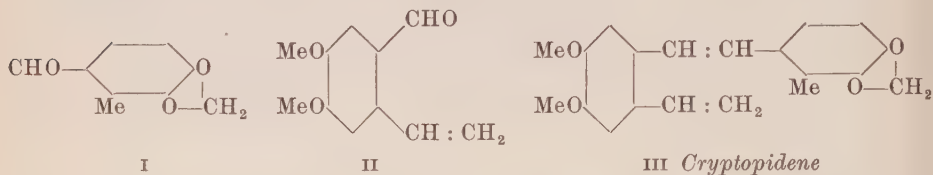
When cryptopine, dissolved in dilute sulphuric acid, is boiled with sodium amalgam, it is reduced to dihydrocryptopine,[1] $C_{21}H_{25}O_5N$, m.p. 187°–188°, which on treatment with acetyl chloride or phosphoryl chloride yields two isomeric quaternary chlorides (α- and β-) of *iso*dihydrocryptopine, $C_{21}H_{24}O_4NCl$. This recalls the similar behaviour of l-canadine (p. 219), and of tetrahydroberberine benzyl- and metho-chlorides (p. 219). These two quaternary chlorides of *iso*dihydrocryptopine are isomeric with those of methyltetra-hydroberberine, and differ only in the interchange of position between the dioxymethylene and the two methoxy groups, and careful com-parison of the two pairs of isomerides and their derivatives shows complete parallelism between the two ; thus the two cryptopine quaternary chlorides yield two anhydrocryptopines, *A*, m.p. 178°, and *B*, m.p. 127°, corresponding to the two anhydrotetrahydro-berberines (p. 219).

On these and other grounds Perkin represents cryptopine and dihydrocryptopine by the following formulæ :

Cryptopine   *Dihydrocryptopine*
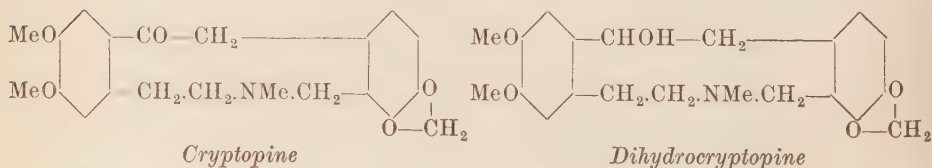
The change of cryptopine to the quaternary chlorides of *iso*-

<hr>

[1] *Cf.* Danckwortt, *Arch. Pharm.* 1912, **250**, 644.

dihydrocryptopine can then be shown by the following partial formulæ :
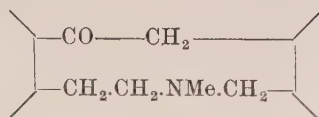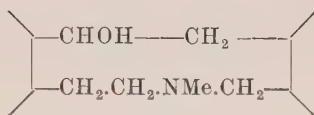
Cryptopine   *Dihydrocryptopine*
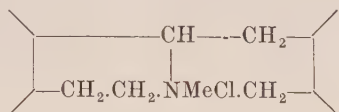
iso*Dihydrocryptopine chloride*

and the formation of the two anhydrodihydrocryptopines as follows :
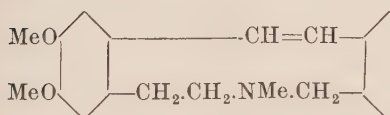
A ← *Anhydrodihydrocryptopine* → B
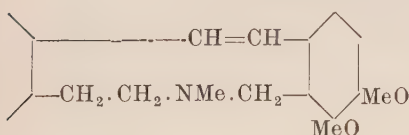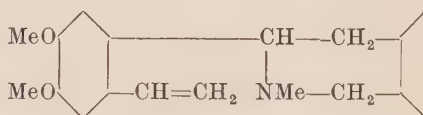
A ← N-*Methyl* iso*tetrahydroberberines* → B
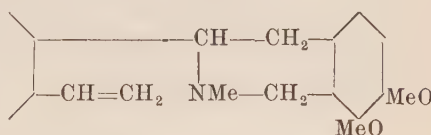
This parallelism between the derivatives of berberine and cryptopine has been fully investigated by Perkin in two particularly interesting directions. The formulæ assigned to the two parent alkaloids and to the chlorides of *iso*cryptopine and berberinium represent cryptopine as related to an alkaloid isomeric with berberinium hydroxide and having formula III, which Perkin has named
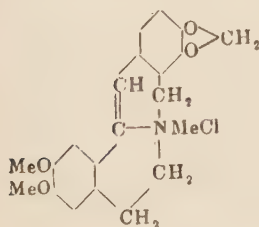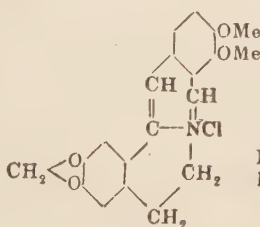
I iso*Cryptopine*   II *Berberinium*   III epi*Berberinium*
chloride   *chloride*   *hydroxide*

*epi*BERBERINE, and which he has prepared by demethylating

*iso*cryptopine chloride, producing dihydroanhydro*epi*berberine (which closely resembles dihydroanhydroberberine) from which *epi*berberine can be obtained by the action of mild oxidising agents such as iodine or mercuric acetate.[1]

The reverse change, viz., the conversion of berberine derivatives by *N*-methylation into substances similarly constituted to corresponding derivatives of cryptopine, was achieved by the methylation of dihydroanhydroberberine, which was thus transformed into the methochloride which corresponds to *iso*cryptopine chloride and proves to resemble it closely in character and reactions.[2]

Dihydroanhydroberberine methochloride

iso*Cryptopine chloride*
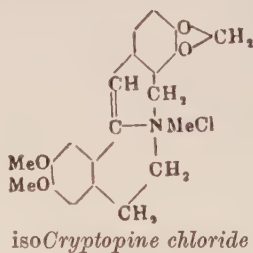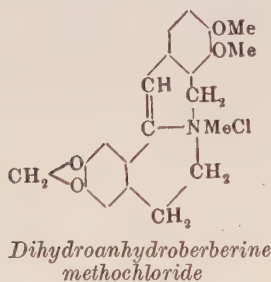
And from this a number of new substances closely resembling the corresponding cryptopine derivatives have been prepared.

Protopine (*Macleyine, Fumarine*), $C_{20}H_{19}O_5N$.   This alkaloid was first isolated by Hesse from opium, but has since been found in a great variety of plants, including the following : *Chelidonium majus, Stylophorum diphyllum, Sanguinaria canadensis, Escholtzia californica, Glaucium luteum, Bocconia* (*Macleya*) *cordata,* and *frutescens, Argemone mexicana, Adlumia cirrhosa, Dicentra* spp., *Corydalis vernyi, C. ambigua, C. tuberosa,* and *Fumaria officinalis.* The best source is probably *Dicentra spectabilis.*[3]

The crude alkaloid (p. 258) is purified by conversion into the sulphate, reprecipitation by ammonia, and crystallisation from chloroform by addition of a little alcohol. It forms monoclinic crystals, m.p. 208°, $[\alpha]_D = 0°$, dissolves readily in chloroform (1 in 15), less so in alcohol (1 in 1,000), acetone or ammonia solution. The hydrochloride, B.HCl, forms slightly soluble prisms ; the platinichloride and aurichloride (m.p. 198°) are amorphous. The base dissolved in acetic acid gives with strong sulphuric acid a blue-violet

[1] *Trans. Chem. Soc.* 1918, **113,** 492.

[2] *Ibid.* p. 722.

[3] Danckwortt, *Arch. Pharm.* 1912, **250,** 590. This paper includes a bibliography and a *résumé* of the botanical distribution of protopine.

solution, becoming more intense and finally changing to red on adding water ; sulphovanadic acid gives a reddish-violet colour changing to deep blue. Protopine, according to Danckwortt,[1] contains two dioxymethylene groups and a non-reactive carbonyl group, and differs from cryptopine by the substitution of a second dioxymethylene group for two methoxyls.

He provisionally represented it as 2-methyl-6 : 7-dioxymethylene- 1-o-methylpiperonyl-1 : 2 : 3 : 4-tetrahydro*iso*quinoline.

The accuracy of these suggestions was to a certain extent confirmed by W. H. Perkin,[2] who, on the ground of the close similarity of its reactions to those of cryptopine, assigned to it the annexed formula :
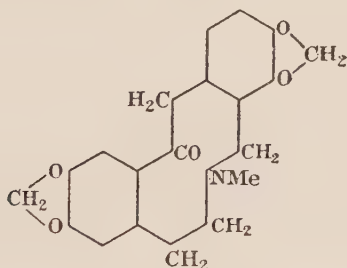
Protopine (Perkin)

Protopine is converted into *iso*protopine chloride, $C_{20}H_{18}O_4NCl$, m.p. 215° (*decomp.*), by the action of phosphoryl chloride, and into *iso*-protopine disulphate, $C_{20}H_{18}O_4N . HSO_4 . H_2SO_4$, m.p. 247° (*decomp.*), by the action of sulphuric acid in presence of acetic acid ; the chloride, when boiled with potassium hydroxide in methyl alcohol, yields anhydroprotopine, $C_{20}H_{17}O_4N$, m.p. 114°–115°. Protopine methosulphate (m.p. 252°, *decomp.*) is decomposed by methyl-alcoholic potassium hydroxide, yielding two methylprotopines, α (m.p. 144°–145°) and γ (m.p. 110°–112°). All these substances correspond exactly with similar derivatives furnished by cryptopine.

MINOR OPIUM ALKALOIDS

Codamine, $C_{20}H_{25}O_4N$. The crude alkaloid, prepared as already described, is purified by boiling with dilute sulphuric acid to remove meconidine, and is then regenerated by adding ammonia solution.

[1] Danckwortt, *Arch. Pharm.* 1912, **250**, 590.
[2] *Trans. Chem. Soc.* 1916, **109**, 875, 1023.

It crystallises from ether in hexagonal prisms, m.p. 126°, but the salts are amorphous. The alkaloid is strongly alkaline, moderately soluble in water, and very soluble in alcohol; it is also dissolved by alkalis. It contains two methoxyl groups and one hydroxyl group. Nitric acid dissolves the alkaloid, forming a dark green liquid. Aqueous solutions are coloured green by ferric chloride.[1]

Pseudopapaverine, $C_{21}H_{21}O_4N$, was obtained by Hesse [2] from commercial papaverine. The hydrochloride, B.HCl, forms monoclinic crystals, m.p. 208°–210° (*decomp.*); the acid oxalate occurs in colourless needles, m.p. 196°. The base, m.p. 147°, is readily soluble in chloroform and more soluble than papaverine in cold dry alcohol. It gives no coloration with sulphuric acid.

Papaveramine, $C_{21}H_{25}O_6N$, obtained by Hesse[2] in purifying papaverine, crystallises in colourless prisms, m.p. 128°–129°, and yields a crystalline hydrochloride, a very soluble acid oxalate, and an amorphous platinichloride. The alkaloid gives an intensely bluish-violet coloration with sulphuric acid.

Meconidine, $C_{21}H_{23}O_4N$. This base was obtained by Hesse [3] by a complex fractionation of the mixed alkaloids precipitated from opium extract by soda solution. It is amorphous, yields amorphous salts, has m.p. 58°, is easily soluble in alcohol, ether, or caustic soda solution, and forms a green solution with sulphuric acid. The alkaloid exerts a mild tetanising action.

Lanthopine, $C_{23}H_{25}O_4N$, was obtained by Hesse [4] in the manner already described (p. 259). It forms a crystalline powder, m.p. 200°, and yields salts which are at first jellies, but finally crystallise. It is sparingly soluble in chloroform and insoluble in alkalis. With sulphuric acid the alkaloid gives a pale violet coloration, changing to brown on heating.

Tritopine, $C_{42}H_{54}O_7N_2$ or $(C_{21}H_{27}O_3N)_2O$. This diacidic alkaloid was isolated by Kauder [5] by treatment of thebaine residues with oxalic acid, whereby the very soluble acid oxalate is formed. The alkaloid crystallises from alcohol in needle-like plates, m.p. 182°, is easily soluble in chloroform or in alkaline solutions, but not in ether, and closely resembles in properties the laudanine group of isomerides. Tritopine is said to be physiologically inactive.

[1] Hesse, *Annalen*, 1870, **153**, 56.
[2] *Journ. prakt. Chem.* 1903 [ii], **68**, 190.
[3] *Annalen*, 1870, **153**, 53.
[4] *Ibid.* 1870, **153**, 53: 1872, *Suppl.* **8**, 280.
[5] *Arch. Pharm.* 1890, **228**, 119.

Rhœadine, $C_{21}H_{21}O_6N$, occurs especially in all parts of the red poppy, *Papaver rhœas*, and in a very minute amount in opium.[1] It crystallises in colourless prisms, m.p. 232° (*decomp.*), 245°–247° (Pavesi), and is sparingly soluble in alcohol, ether, chloroform, or water. It is faintly alkaline to litmus, but does not easily form salts with acids. It gives a purple coloration with moderately strong hydrochloric or sulphuric acid, which disappears on addition of alkali, but returns when the solution is acidified. On treatment with strong acids rhœadine is converted into RHŒAGENINE, $C_{21}H_{21}O_6N$, rectangular leaflets, m.p. 223° (235°–237°, Pavesi), from alcohol, which is strongly basic, and, though tasteless itself, gives bitter salts. The hydriodide forms prisms and is sparingly soluble in water. Rhœadine is not toxic.

PHYSIOLOGICAL ACTION OF OPIUM ALKALOIDS

The foregoing discussion of the opium alkaloids shows that as regards chemical constitution they fall into two main groups : (1) The *morphine* group, including morphine, codeine, thebaine ; and (2) the *narcotine* group, including narcotine, narceine, and papaverine as its principal members. The most characteristic feature of the physiological action of the opium alkaloids is their simultaneous depressing and exciting action on the central nervous system, and in this respect there is no clear line of demarcation between the two groups. The five chief members—morphine, papaverine, codeine, narcotine, and thebaine—all exhibit this peculiarity, and as the series is descended in the order just given the narcotic action diminishes, and the power of reflex stimulation increases until in thebaine a strychnine-like effect is exhibited.

Vahlen [2] has attributed the characteristic action of morphine to the phenanthrene group, and Bergell and Pschorr [3] have pointed out that whilst phenanthrene itself has no action on rabbits, the 2-, 3-, and 9-hydroxyphenanthrenes cause tetanic convulsions, but no narcotic effect. Loeb and Oldenburg state that whilst dihydromorphine and dihydrocodeine resemble the parent alkaloids in action, tetrahydrothebaine no longer causes tetanus, and they connect this property with the presence of an ethylenic linkage,

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[1] *Hesse, Annalen,* 1867, **140,** 145.
[2] *Arch. exp. Path. Pharm.* 1902, **47,** 368.
[3] *Zeit. Physiol. Chem.* 1903, **38,** 16.

supposing that dihydromorphine, but not tetrahydrothebaine, may be reoxidised in the body to the parent base.[1]   According to von Braun, the special properties of morphine and codeine must be associated with the position of the N-atom in relation to the bridged hexamethylene ring.[2]

MORPHINE.   This alkaloid exerts both a depressing and stimulating action on the central nervous system, the former being produced mainly in the brain, the latter mainly in the spinal cord. In the cat there is also some stimulation in the brain, but in man the depressing action dominates the whole nervous system.   Respiration is slowed by morphine ; in many cases it may be deeper at first, though the amount of air taken in per minute is reduced. In the higher animals death ensues from arrest of respiration.   The alkaloid has little effect on the circulation, and this is also true of the peripheral muscles and nerves.   The pupil of the eye is much contracted in morphine poisoning until just before asphyxia, when it is widely dilated.   The alkaloid causes a slight fall in body temperature.

Morphine is excreted mainly by the digestive tract, but after large doses it also occurs in traces in the urine.

It is usually fatal to man in doses of 0·2 to 0·3 grm., but continued use of the drug enables considerable tolerance to be acquired, so that large doses are required to produce any effect.

PAPAVERINE is a comparatively weak poison, but in the nature of its effects stands between morphine and codeine.   It produces light sleep when taken in comparatively small doses, and this does not become deeper when the dose is increased.   On the other hand, the reflex irritability is increased, and large doses may cause some tetanising action.   It has more tendency than either morphine or codeine to slow the heart.   According to Macht and Fisher,[3] the papaverine group of alkaloids are toxic to certain protozoa (*e.g.,* *Paramœcium putrinum*), whereas members of the morphine group are comparatively innocuous, though both groups exert a narcotic or anæsthetic effect on Paramœcium distinct from the toxic action shown by papaverine and its allies.   Macht has also shown that a similar difference is shown by the two groups in their action on smooth muscle, the morphine group exerting a stimulating action

[1] *Verh. Ges. deut. Naturf. A.* 1912 [ii], **2,** 481.

[2] (With Kindler) *Berichte,* 1916, **49,** 2655.

[3] *Journ. Pharm. Exper. Therap.* 1917, **10,** 95.

on the rhythmic contraction and tonicity of smooth muscle from various organs, whilst the papaverine series exert an inhibitory action which was traced to the benzyl group. Benzylmorphine (peronin) is anomalous in its action, due to the opposing influences of the morphine structure and the benzyl group.[1] This work has resulted in the limited use of benzyl alcohol and saligenin as local anæsthetics and benzyl benzoate and similar esters as anti-spasmodics.

CODEINE resembles morphine in its general effect, but its depressant action is less marked and less prolonged, whilst its stimulating action involves not only the spinal cord but also the lower parts of the brain. In small doses in man it induces sleep which is not so deep as that caused by morphine, and in large doses it causes restlessness and increased reflex excitability rather than sleep. The respiration is slowed less than by morphine. The pupil is contracted at first, but is dilated in the excitement stage of the intoxication. The artificial alkaloids, DIONIN (ethylmorphine) and PERONIN (benzylmorphine), somewhat resemble codeine in their action. HEROIN (diacetylmorphine) resembles morphine in its general action, but is stated to affect respiration to a greater extent than morphine, without producing mental depression.

NARCOTINE in general resembles codeine in its action, but is less depressant. It is much less poisonous than either morphine or codeine. It was at one time used in India as a remedy for malaria, but has long been superseded by quinine for this purpose. NARCEINE has been recommended as a hypnotic, but is believed to have very little action when pure, probably owing to the instability of its salts and the insolubility of the alkaloid itself. OXYNARCOTINE is described as a feeble narcotic poison.

THEBAINE stands at the other end of the series from morphine. In thebaine the depressing action on the central nervous system has almost disappeared, and this alkaloid resembles strychnine rather than morphine in its action, though it is much less active than strychnine.

Thebaine is, however, convertible into *oxydihydrocodeinone*,[2]

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[1] *Journ. Pharm. Exper. Therap.* 1918, **11,** 389, 419. *Cf.* Pal and Popper, *Biochem. Zeits.* 1913, **57,** 492.

[2] Freund and Speyer, *Munch. Med. Woch.* 1917, **64,** 380. For other substances possibly also belonging to this series, *see* German Patent 365,683 (*Chem. Soc. Abstr.* 1923 [i], 940).

which is stated to be a powerful narcotic that can be used to produce a hypnotic condition suitable for the performance of severe surgical operations. The hydrochloride is known as "eukodal." The substance is produced by oxidising thebaine with hydrogen peroxide and has the composition represented by the formula, $C_{18}H_{19}O_4N$. In its formation the following changes in the thebaine molecule are supposed to occur (the numerals correspond with those in the formula on p. 275) :

$$\overset{\cdot C \cdot}{\underset{\text{Thebaine}}{\underset{5}{>}\overset{5}{C}-\overset{6}{C}(OCH_3)=CH-\overset{\parallel}{C}H}} \rightarrow \underset{\text{Oxydihydrocodeinone}}{\overset{\cdot CH \cdot}{>\overset{5}{C}-\overset{6}{C}O-CH(OH)-\overset{\mid}{C}H_2}}$$
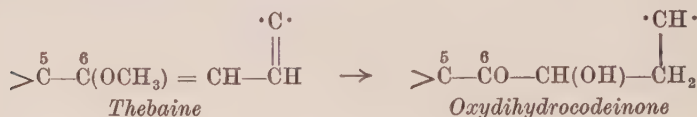
Very few of the rarer opium alkaloids have been completely examined physiologically. LAUDANOSINE and LAUDANINE are stated to be similar to thebaine in their action, laudanine being the more poisonous. MECONIDINE is stated to exert an effect similar to that of thebaine, but to be much weaker. CRYPTOPINE, PROTOPINE and TRITOPINE produce in frogs narcosis similar to that caused by morphine. In mammals there is no depression, but restlessness and convulsions are produced. These alkaloids are also stated to paralyse the sensory nerve terminations somewhat like cocaine. Their action on the heart is more marked than that of narcotine and papaverine.

Of the derivatives of the opium alkaloids, two are of special importance in medicine, viz., apomorphine and cotarnine.

APOMORPHINE. In the conversion of morphine into apomorphine the depressing action on the central nervous system is almost wholly lost, but the stimulant action remains, and is exercised over the whole central nervous system, but especially on the medulla. In very small doses apomorphine may not produce vomiting, though the secondary symptoms—such as increased perspiration —which usually accompany this may be shown. The emetic action is due to direct action on the medulla oblongata and not to irritation of the stomach. According to Hildebrandt [1] thebaine antagonises the emetic action of apomorphine in dogs, and Harnack and Hildebrandt [2] have shown that α- and β- chloromorphides are also antiemetics, the former being the more powerful.

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[1] *Arch. exp. Path. Pharm.* 1911, **65**, 54.
[2] *Ibid.* p. 38.

COTARNINE. This decomposition product of narcotine is used in medicine as a styptic in uterine hæmorrhage, but is less effective than the more expensive hydrastinine and is said to produce its effect in a different way.

ALKALOIDS OF OTHER PAPAVER SPECIES

The following species of Papaver have also been examined, but in most cases little is known regarding the alkaloids they contain.

Papaver dubium. This was examined by Pavesi [1] who isolated from it APOREINE, $C_{18}H_{16}O_2N$, yellowish-green monoclinic prisms, m.p. 88°–89°, yielding crystalline salts, B.HCl, m.p. 230°, and APOREIDINE, crystalline, m.p. 176°–178°. The former is described as a tetanising poison similar to thebaine.

P. hybridum, contains rhœadine (*see* p. 305), and a second base.[2]

P. lateritum, contains an amorphous phenolic alkaloid.[3]

P. Rhœas, contains rhœadine [2] (*see* p. 305).[4]

P. orientale. This plant was examined in 1911 by Gadamer and Klee,[3] who obtained from it a crystalline phenolic alkaloid, m.p. 204°–205° (*iso*thebaine), but the same authors have recently reinvestigated it and isolated a series of alkaloids of which the most interesting is *iso*thebaine,[5] the others being thebaine (p. 266), glaucidine and two phenolic bases and one non-phenolic base.[6]

*iso***Thebaine,** $C_{19}H_{21}O_3N$, forms highly refractive colourless rhombic crystals from ether or alcohol, m.p. 203°–204°, $[\alpha]_D^{18} + 285 \cdot 1°$. The sulphate, $B_2.H_2SO_4$, m.p. 120°–121° (*decomp.*) and the acid *l*-tartrate are well-crystallised salts, but the hydrochloride is difficult to isolate owing to its ready solubility. The alkaloid is distinguished from all other papaveraceous alkaloids by giving an intense violet colour with nitric acid.

*iso*Thebaine behaves as a phenol and contains one phenolic hydroxyl group, two methoxyl groups and a methylimino group. In its general behaviour it resembles morphothebaine and apomorphine, and like these alkaloids yields a diacetyl derivative,

[1] *Chem. Soc. Abstr.* 1905 [i], 368 ; 1907 [i], 870 ; *Gazzetta,* 1914, **44,** [i], 398 ; and *Riv. Sanit. Piacontina,* 1913, vol. 2.

[2] Pavesi, *Chem. Soc. Abstr.* 1906 [ii], 483.

[3] Gadamer and Klee, *Arch. Pharm.* 1911, **249,** 39.

[4] Hesse, *Annalen,* 1866, **140,** 146.

[5] Klee, *Arch. Pharm.* 1914, **252,** 211.

[6] Gadamer, *ibid.* p. 274.

colourless leaflets, m.p. 80°–85°.　With diazomethane it forms *iso*-thebaine methyl ether, amorphous, $[\alpha]_D + 234\cdot5°$ in chloroform, which gives a crystalline hydrogen *l*-tartrate, m.p. 226°–227° (*decomp.*), $[\alpha]_D + 143°$ in water.　This ether closely resembles morphothebaine methyl ether, but from its rotation is not stereoisomeric with it.

On exhaustive methylation, using methyl sulphate, there were obtained eventually trimethylamine and a trimethoxyvinylphenanthrene from which a trimethoxyphenanthrene, yielding a picrate, m.p. 160°, which is very probably that of 3 : 4 : 5 : trimethoxyphenanthrene, and if this is correct *iso*thebaine methyl ether must be dimethylmorphothebaine, and in *iso*thebaine the — OH group must be in position 4 or 5, probably 4.

iso*Thebaine*
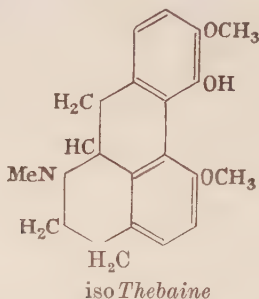
Glaucidine was obtained in such minute quantity that its empirical composition could not be determined, but it is phenolic in character, and gives the characteristic colour reactions of the glaucine group (*cf.* p. 243).　It melts at 209°–210°, and, once obtained crystalline, is so difficult to dissolve in ordinary solvents that it could not be recrystallised.

OTHER *ISO*QUINOLINE ALKALOIDS

A number of the alkaloids already described, *e.g.*, berberine, protopine, chelidonine, the homochelidonines and sanguinarine, occur in other plants sometimes in association with other alkaloids.　The most important of these are given in the following table.　Little is known regarding these " other alkaloids," but, as their associates are *iso*quinoline derivatives, they are most conveniently described with them.

Name of Plant.	Constituents already Described.	Other Constituents.
Adlumia cirrhosa.[1]	β-Homochelidonine (p. 250), protopine (p. 302).	Adlumine,$HO.C_{37}H_{34}O_9N.(OMe)_2$; m.p. 188°, $[a]_D + 39·88°$; orthorhombic crystals. Adlumidine, $C_{30}H_{29}O_9N$, m.p. 234°; small square plates. Fifth alkaloid, m.p. 176°–177°; crystalline.
Argemone mexicana.[2]	Protopine, berberine (p. 208).	" Argemonine " is impure protopine.
Bocconia cordata.	β-Homochelidonine, protopine, chelerythrine (p. 247), sanguinarine (p. 252).	See p. 250 for list of references.
Eschscholtzia californica.[3]	β- or γ-Homochelidonine (p. 250), protopine, chelerythrine, sanguinarine.	Alkaloid (*a*), rosettes of thin prisms; m.p. 242°–243°. Alkaloid (*b*), m.p. 217°. Ionidine, $C_{19}H_{25}O_4N_4$, m.p. 154°–155°, is the only alkaloid present (Brindejonc).
Fumaria officinalis.[4]	Protopine.	—
Sanguinaria canadensis.[5]	β- and γ-Homochelidonine, protopine, chelerythrine, sanguinarine.	—
Stylophorum diphyllum.[6]	Chelidonine, protopine, sanguinarine.	Stylopine, $C_{19}H_{19}O_5N$; colourless needles; m.p. 202°; lævorotatory; tertiary base, contains no methoxyl. Diphylline, m.p. 216°.

[1] Schlotterbeck, *Amer. Chem. Journ.* 1900, **24**, 249; *Pharm. Archives*, 1903, **6**, 17.

[2] Schlotterbeck, *Pharm. Rev.* 1901, **19**, 458.

[3] Fischer, *Amer. Journ. Pharm.* 1901, **239**, 421; with Tweeden, *Pharm. Archives*, 1902, **5**, 117; Brindejonc, *Bull. Soc. chim.* 1911 [iv], **9**, 97.

[4] Dana, *Mag. Pharm.* 1829, **23**, 125.

[5] König and Tietz, *Arch. Pharm.* 1893, **231**, 145; Fischer, *ibid.* 1901, **239**, 409; Bauer and Hedinger, *ibid.* 1920, **258**, 167.

[6] Schlotterbeck and Watkins, *Pharm. Rev.* 1901, **19,** 453.

VI. INDOLE GROUP

INDOLE, which may be regarded as benzene condensed with pyrrolidine, is one of the products of putrefaction of protein, but has been found in the volatile oils distilled from jasmine and orange flowers,[1] whilst its higher homologue, scatole (3-methylindole), which also accompanies it among putrefaction-products of protein occurs in the wood of *Celtis reticulosa*.[2]

Hypaphorine, $C_{14}H_{18}O_2N_2 . 2H_2O$, was first obtained by Greshoff [3] from the seeds of *Erythrina hypaphorus*, grown as a shade tree in coffee plantations in Java, and was further investigated by van Romburgh and Barger.[4] It forms large monoclinic crystals from water, melts at 255° (*dry*), has $[\alpha]_D + 91°$ to 93°, and yields a characteristic, sparingly soluble nitrate, $B . HNO_3$, m.p. 215°–220°. When heated with aqueous potassium hydroxide it yields trimethylamine and indole.

Hypaphorine is formed when tryptophan (3-indole-α-aminopropionic acid) is boiled with methyl iodide in presence of sodium hydroxide in methyl alcohol, and the resulting product heated at 100° for a few minutes with dilute sodium hydroxide solution. It is regarded, therefore, as α-trimethyl-3-indolepropiobetaine, and its relationship to tryptophan is shown by the following formulæ :

Hypaphorine   *Tryptophan*

Hypaphorine produces increased reflex irritability in frogs in doses of 0·012 to 0·015 grm., but has very little action on rats or pigeons.

[1] A. Hess, *Berichte*, 1899, **32**, 2611.
[2] Dunstan, *Proc. Roy. Soc.* 1890, **46**, 211.
[3] *Meded. uit's Lands. Plant.* 1890, **7**, 29.
[4] *Proc. K. Akad. Weten. Amst.* 1911, **13**, 1177 ; *Trans. Chem. Soc.,* 1911, **99**, 2068.

ALKALOID OF *ARARIBA RUBRA* AND *SYMPLOCOS RACEMOSA*

The alkaloid ARIBINE, $C_{23}H_{20}N_4.8H_2O$, obtained by Rieth and Wohler [1] from the bark of this plant has been shown by Späth [2] to be identical with harman, $C_{12}H_{10}N_2$, m.p. 237°–238° (*in vacuo*). The aurichloride, m.p. 211°–213° (*decomp.*), platinichloride, m.p. above 280° (*in vacuo*), picrate, m.p. above 250° (*decomp.*), were prepared and compared with those of harman made from harmine (p. 317).

The same applies to LOTURINE found by Hesse [3] in *Symplocos racemosa*, and COLLOTURINE, which accompanies loturine, is probably a second crystalline form of harman. [4]

ALKALOIDS OF *EVODIA RUTÆCARPA*

Evodia meliæfolia has been mentioned already as one of the sources of berberine. The allied plant (*E. rutæcarpa*) contains, according to Asahina, [5] two alkaloids, evodiamine and rutæcarpine, belonging to the indole group.

Evodiamine, $C_{19}H_{17}ON_3$, yellowish leaflets, m.p. 278°, $[\alpha]_D^{15} + 352°$ (in acetone), is a weak base, insoluble in dilute acids. When heated in alcohol with hydrochloric acid it absorbs water, being converted into evodiamine hydrate (*iso*evodiamine), $C_{19}H_{19}O_2N_3$, rhombic leaflets, m.p. 146°–147°, $[\alpha]_D$ 0°, and forms a hydrochloride, $C_{19}H_{17}ON_3.HCl$, crystallising from alcohol in hexagonal or rhombic plates, m.p. 255°–256° or 265°–267° (*dry*), and a nitrosoamine, m.p. 120°. Acetic anhydride at 150° reconverts " isoevodiamine " to *optically inactive* evodiamine. Evodiamine is decomposed by boiling alcoholic potassium hydroxide into N-methylanthranilic acid and a base, $C_{11}H_{10}N_2$, believed to be 3 : 4-dihydro-5-carboline. [6] Evodiamine hydrate undergoes fission under like conditions into carbon dioxide, N-methylanthranilic acid and a base, $C_{10}H_{12}N_2$, which is regarded as 2-β-aminoethylindole, since it yields indole-2-carboxylic acid on fusion with potash.

[1] *Annalen,* 1860, **120,** 247.

[2] *Monats.* 1919, **40,** 351.

[3] *Annalen,* 1879, 673.

[4] Späth, *Monats.* 1920, **41,** 297.

[5] (With Kashiwagi) *J. Pharm. Chim.* 1916 [vii], **14,** 54 ; (with Mayeda) *J. Pharm. Soc. Japan,* 1916, No. 416 (*Chem. Soc. Abstr.* 1921 [i], 48). For a complete account *see* Asahina, Ishio, Kashiwagi, Mayeda and Fujita (*Acta phytochimica,* Tokyo, **1,** 67).

[6] For explanation of this term, *see Trans. Chem. Soc.* 1919, **115,** 970.

Rutæcarpine, $C_{18}H_{13}ON_3$, crystallises in small yellow plates, m.p. 258°, and is decomposed by potassium hydroxide in boiling amyl alcohol, yielding anthranilic acid and 2-β-aminoethylindole-3-carboxylic acid, $C_{11}H_{12}O_2N_2$, silky crystals, m.p. 257°. Unlike evodiamine rutæcarpine yields a monoacetyl and a monobenzoyl derivative melting at 184°–186° and 194° respectively.[1]

To these alkaloids, Asahina and Mayeda assigned the following formulæ, based on the reactions just described :
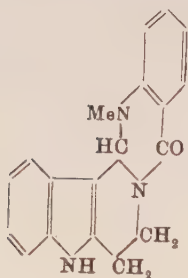
Evodiamine　　　*Evodiamine hydrate*　　　*Rutæcarpine*
　　　　　　　　　("*iso*Evodiamine")

Kermack, Perkin and Robinson [2] have pointed out that the evidence so far produced does not completely rule out the following formula for evodiamine, which would bring this alkaloid into line with harmine (p. 316).
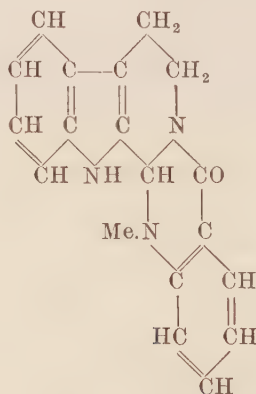
Evodiamine (K.P.R.)

[1] (With Fujita) *J. Pharm. Soc. Japan*, 1921, 863.
[2] *Trans. Chem. Soc.* 1921, **119**, 1615.

ALKALOIDS OF *PEGANUM HARMALA*

The seeds of this plant contain three alkaloids, harmaline, $C_{13}H_{14}ON_2$, obtained by Goebel,[1] harmine, $C_{13}H_{12}ON_2$, isolated by Fritsche,[2] and harmalol, $C_{12}H_{12}ON_2$, first prepared by O. Fischer.[3]

The alkaloids may be extracted by percolating the finely ground seeds with very dilute sulphuric acid, adding salt to the liquors to precipitate the mixed alkaloidal hydrochlorides, which, after washing with brine, are dissolved in water, the solution decolourised with animal charcoal, warmed to 50°, and fractionally precipitated with ammonia, harmine coming out first and harmaline only in presence of a considerable excess of ammonia. Harmine is purified by crystallisation from methyl alcohol containing benzene, and harmaline by crystallisation from alcohol or benzene. If harmalol is to be isolated the original acid extract is concentrated, harmine and harmaline precipitated with caustic soda and separated as described above. The filtrate is acidified, then made alkaline with sodium carbonate, the harmalol extracted with chloroform and recrystallised from water or alcohol. The seeds contain about 4 per cent. of alkaloids, of which about two-thirds is harmaline.

Harmaline, $C_{13}H_{14}ON_2$, crystallises from alcohol or benzene in colourless, glancing prisms, m.p. 250° (*decomp.*), $[\alpha]_D$ 0°, is readily soluble in hot alcohol, much less so in cold alcohol, ether or water. The hydrochloride, $B.HCl.2H_2O$, forms slender yellow needles, sparingly soluble in brine or hydrochloric acid ; the platinichloride is microcrystalline. Harmaline forms a characteristic mercurichloride and a crystalline acid chromate, which is insoluble in water. Solutions of salts of the base give with potassium cyanide a precipitate of harmaline hydrocyanide, $B.HCN$, which reacts as a simple base and forms a hydrochloride, $C_{14}H_{15}ON_3.HCl$. Harmaline behaves as a secondary amine, giving an acetyl derivative, m.p. 204°– 205°, colourless needles ; and with methyl iodide N-methylharmaline hydriodide, from which N-methylharmaline, needles, m.p. 162°, can be obtained by the action of baryta, and this by further action of methyl iodide yields methylharmaline methiodide. The oxygen atom in harmaline is present as a methoxyl group, and, on boiling with hydrochloric acid, the phenolic base, HARMALOL, $C_{12}H_{12}ON_2$. $3H_2O$, which also occurs naturally in the seeds,[4] is obtained. It

[1] *Annalen*, 1841, **38**, 363.

[2] *Ibid.* 1847, **64**, 365.

[3] *Berichte*, 1885, **18**, 400 ; 1889, **22**, 637 ; 1897, **30**, 2481.

[4] O. Fischer, *Chem. Soc. Abstr.* 1905 [i], 405.

crystallises from water in brown needles, m.p. 212° (*decomp.*), and is readily soluble in chloroform, acetone, or hot water, sparingly so in cold water or benzene, but readily in alkaline liquids. It oxidises in the air. On reduction harmaline yields the same product as harmine, viz., tetrahydroharmine, $C_{13}H_{16}ON_2$, m.p. 199°, and on gentle oxidation is converted into harmine, so that it is a dihydroharmine.

Harmine, $C_{13}H_{12}ON_2$, crystallises from methyl alcohol in colourless rhombic prisms, m.p. 257°–259°, $[\alpha]_D$ 0°, and is sparingly soluble in water, alcohol, or ether. The hydrochloride, platinichloride, acid chromate, and oxalate are all well crystallised. The salts show a deep blue fluorescence in dilute solution. Harmine behaves as a monoacidic, secondary base, giving with methyl iodide first methylharmine and then methylharmine methiodide. When boiled with hydrochloric acid, harmine yields methyl chloride and a new base, HARMOL, $C_{12}H_{10}ON_2$, m.p. 321°, which corresponds with harmalol, $C_{12}H_{12}ON_2$, similarly formed from harmaline.[1]

Constitution of Harmine and Harmaline. It has already been pointed out that harmaline is a dihydroharmine, and that the oxygen atom is present as methoxyl in both cases. Our knowledge of the constitution of the two alkaloids is mainly due to the work of O. Fischer and his colleagues, and more recently to the researches of Perkin and Robinson.

On oxidation with chromic acid both alkaloids yield harminic acid,[2] $C_8H_6(COOH)_2N_2$, which has the properties of an *o*-dicarboxylic acid. This when heated *in vacuo* loses in two stages the two carboxyl groups, and furnishes APOHARMINE, $C_8H_8N_2$, m.p. 183°, a secondary base yielding well-crystallised salts (aurichloride, m.p. 240°, picrate, m.p. 247°).

With strong nitric acid harmaline gives, in addition to harminic acid, *m*-nitroanisic acid.[3]

Harminic acid, on further oxidation by dilute nitric acid, yields *iso*-nicotinic acid [4] (pyridine-4-carboxylic acid). Since *m*-nitroanisic acid is also formed by the oxidation of harmaline, there must be present in the latter a methoxybenzene ring in addition to the structural residues found in harminic acid. Further, Perkin and Robinson [5] showed that harmine condenses with benzaldehyde to form benzylideneharmine, $C_{12}H_9ON_2.CH : CH.C_6H_5$ (a reaction which is typical

[1] Fischer and Tauber, *Berichte*, 1897, **30**, 2482.
[2] Fischer and Tauber, *ibid.* 1885, **18**, 403.
[3] Fischer and Boesler, *ibid.* 1912, **45**, 1934.
[4] Fischer, Angermann and Diepolder, *ibid.* 1914, **47**, 99.
[5] *Trans. Chem. Soc.* 1912, **101**, 1778.

of substances containing a pyridine ring with a methyl group in the α-position to the nitrogen atom), and this substance on oxidation yields norharmine, $C_{12}H_{10}ON_2$, which possesses properties similar to those of harmine. The formulæ of harmine and its two degradation products may, therefore, be written thus :

$$MeO.C_6H_3.C_5H_2Me(N.NH)$$

Harmine

$$CO_2H.C \underset{CO_2H.C}{\overset{\parallel}{\diagdown}} C_5H_2Me(N.NH)$$

Harminic acid

$$\underset{CH}{\overset{CH}{\diagdown}} C_5H_2Me(N.NH)$$

Apoharmine
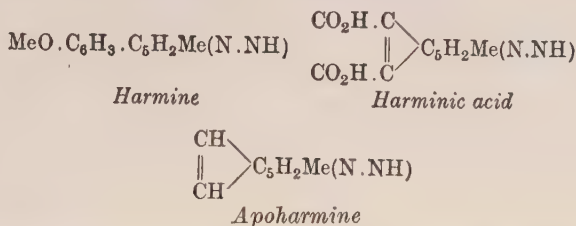
Perkin and Robinson suggested in 1912 that harmine and harmaline probably had a structure composed of three rings—pyridine, pyrrole, and benzene fused together—but the sequence of these rings was in doubt. Fischer's observations in 1912 and 1914, that *m*-nitroanisic acid and *iso*nicotinic acids are produced by the oxidation of harmine, indicated that the benzene and pyridine rings occupy terminal positions, but the first definite evidence of the presence and position of the pyrrole nucleus was afforded by Perkin and Robinson's [1] discovery that the base harman, $C_{12}H_{10}N_2$, which Fischer [2] obtained by the elimination of methoxyl from harmine was identical with a base obtained by Hopkins and Cole [3] by the oxidation of tryptophan with ferric chloride.

Tryptophan : $CH_2.CH(NH_2).CO_2H$
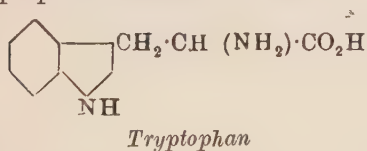
Harman

From this formula for harman, various expressions for harmine and harmaline are derivable, and of these the following have now been adopted by Perkin and Robinson :

Harmine   *Harmaline*
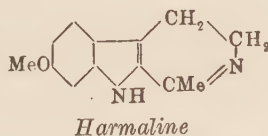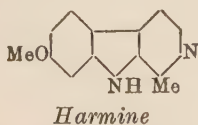
[1] *Trans. Chem. Soc.* 1919, **115,** 967. *Cf.* p. 933, where the genesis of the harmine formula is fully discussed.

[2] *Chem. Soc. Abstr.* 1905 [i], 405. *Cf.* Perkin and Robinson, *loc. cit.,* p. 971.

[3] *Journ. Physiol.* 1903, **29,** 451.

The mechanism of the conversion of tryptophan into harman [1] has been investigated by Kermack, Perkin and Robinson, and the validity of the formulæ for harmine and harmaline built upon it has been confirmed by the synthesis of two substances closely allied to these two alkaloids. Thus Kermack, Perkin and Robinson,[1] have prepared norharman (1) by oxidising benzylideneharman with potassium permanganate in pyridine and heating the resulting norharmancarboxylic acid in glycerol : (2) condensing tryptophan with formaldehyde ; (3) converting 1-methylindole-2-carboxyacetalylamide (ɪ) into 3-keto-1-methyl-3 : 4-dihydro-4-carboline [2] (ɪɪ) (by warming it with alcoholic hydrogen chloride) and distilling the latter with zinc dust. Processes 2 and 3 may be represented thus :

(2) Tryptophan $+ CH_2O$ → Norharman

(3) I → II
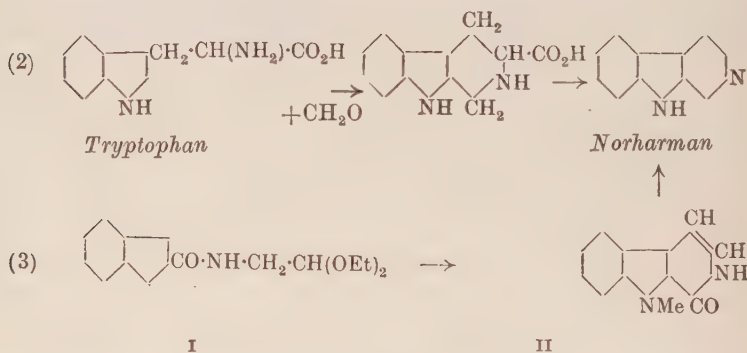
The same authors [3] have prepared N-methyltetrahydronorharmine in the following ways :

1. 6-Methoxyindole-2-carboxylic acid (ɪ) was converted into the acid chloride, and this, treated with methylaminodimethylacetal, yielding 6-methoxyindole-2-carboxydimethylacetalylmethylamide (ɪɪ), which, on boiling with alcoholic hydrogen chloride gave 11-methoxy-3-keto-4-methyl-3 : 4-dihydro-4-carboline (ɪɪɪ), and this, on reduction with sodium in normal butyl alcohol, furnished N-methyltetrahydronorharmine (ɪᴠ).

2. Harmaline methosulphate, on oxidation with potassium permanganate, yields a substance, $C_{13}H_{14}O_2N_2$, which proved to be

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[1] It can also be made by condensing tryptophan with acetaldehyde, *Trans. Chem. Soc.* 1921, **119**, 1604, 1617.

[2] For definition and numbering of " carboline " *see Trans. Chem. Soc.* 1919, **115**, 970.

[3] *Trans. Chem. Soc.* 1922, **121**, 1872.　For further syntheses in this series, *see ibid.* 1924, **125**, 626, 657.

keto-*N*-methyltetrahydronorharmine (v), and on reduction with sodium in butyl alcohol gave *N*-methyltetrahydronorharmine (IV).

rmaline Methosulphate
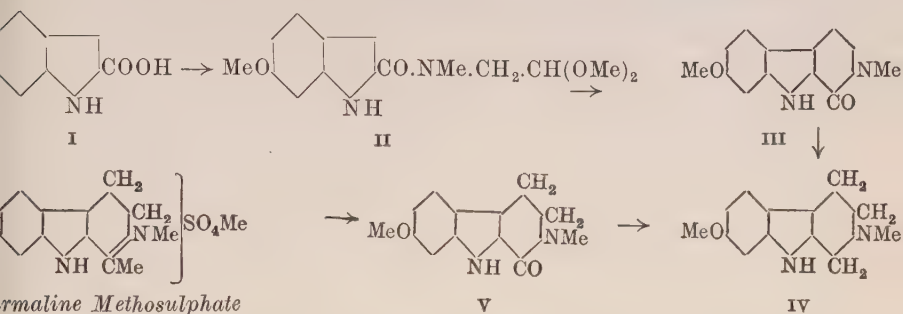
Physiological Action. *Peganum harmala* seeds have been used as a remedy for tapeworm in man. Flury [1] states that harmaline has an anthelmintic action, probably by paralysing the musculature of the parasites, and that harmine, harmaline, and tetrahydroharmine have a paralysing action on frogs, whilst apoharmine causes increased reflex irritability and tetanus. Harmine and harmaline paralyse the skeletal and cardiac muscles of the frog. In warm-blooded animals, according to the same author, harmine and harmaline cause convulsions, increase of saliva, interference with respiration, and depression of temperature.

According to Gunn,[2] harmaline resembles quinine in being more toxic to mammals than to frogs. He also finds that in mammals harmine produces a fall in blood-pressure due to weakening of heart contractions, and cardiac failure is the chief cause of death. It stimulates respiration in small doses, but in large doses paralyses it. The minimal toxic dose for rabbits is 0·23 grm. per kilogramme of body weight. Gunn and Marshall [3] have found that harmine and harmaline are useful in malaria, both being less efficient in acute cases than quinine, but harmine was remarkably successful in a few cases of relapsing malaria.

[1] *Arch. exp. Path. Pharm.* 1910, **64,** 105.
[2] *Trans. Roy. Soc. Edin.* 1910, **47** [ii], 245 ; 1912, **48** [i], 83.
[3] *Proc. Roy. Soc. Edin.* 1920, **40,** 140.

VII. GLYOXALINE GROUP

ALKALOIDS OF *PILOCARPUS* SPP. (JABORANDI)

JABORANDI leaves were first employed therapeutically in 1874 by Dr. Coutinho, of Pernambuco, by whom they were sent to Europe. At first the leaves were wrongly referred in Europe to *P. pennatifolius*, but Holmes showed that up to 1893 the jaborandi of commerce was obtained almost wholly from *P. Jaborandi*. Since 1896 the leaves of neither species have been obtainable in commerce, and their place has been taken by the leaves of *P. microphyllus*. The leaves of *P. spicatus* and *P. trachylophus* have also appeared on the English market from time to time.

The drug was first examined in 1875 by Hardy,[1] who isolated from it pilocarpine. The same base was prepared independently by Gerrard,[2] who succeeded in obtaining several of its salts in a crystalline condition. Some years later Harnack and Meyer[3] isolated a second alkaloid, jaborine, which, according to Jowett,[4] is merely a mixture of the various alkaloidal constituents of the drug. In 1885 Harnack and Meyer[5] discovered a third alkaloid, pilocarpidine, in jaborandi, and the existence of this alkaloid has been confirmed by Jowett,[4] though it does not occur in the jaborandi of present-day commerce. In 1897 a fourth alkaloid was isolated by Petit and Polonovski[6] from the leaves of *Pilocarpus microphyllus*, and named by them "pilocarpidine" [β-pilocarpine (Brühl), *iso*pilocarpine (Jowett)] apparently under the impression that it was identical with Harnack and Meyer's base. A fifth alkaloid, pilosine, has been obtained by Pyman. Petit and Polonowski have stated that *P. spicatus* leaves contain ψ-pilocarpine and ψ-jaborine.

The principal facts relating to the alkaloidal constituents of the leaves of *Pilocarpus* spp. are shown in the following table :

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[1] *Bull. Soc. chim.* 1875 [ii], **24**, 497.
[2] *Pharm. Journ.* 1875 [iii], **5**, 865, 965 ; 1877, **7**, 255.
[3] *Annalen*, 1880, **204**, 67.
[4] *Trans. Chem. Soc.* 1900, **77**, 474, 851 ; 1901, **79**, 581, 1331.
[5] *Chem. Centr.* 1885, 628.
[6] *Journ. Pharm.* 1897 [vi], **5**, 370, 430, 475 ; **6**, 8.

Name of plant.	Commercial name.	Synonym.	Constituents.	Amount of total alkaloid per cent.	Amount of crystalline pilocarpine nitrate obtained per cent.
P. Jaborandi (Holmes)	Pernambuco jaborandi.	Formerly regarded as *P. pennatifolius.*	Pilocarpine *iso*pilocarpine(?) pilocarpidine	0·72[1]	0·67
P. pennatifolius (Lemaire)	Paraguay jaborandi.	*P. selloanus.*	Pilocarpine *iso*pilocarpine.	0·2 to 0·3	—
P. microphyllus (Stapf)	Maranham jaborandi.	—	Pilocarpine *iso*pilocarpine pilosine	0·765 to 0·783[2]	0·45[1]
P. racemosus	Guadeloupe jaborandi.	—	Pilocarpine	—	0·12[3]
P. trachylophus (Holmes)	Ceara jaborandi.	—	Not known	0·4[1]	—
P. spicatus (St. Hilaire)	Aracati jaborandi.	—	ψ-Pilocarpine ψ-Jaborine	0·16[1]	—

The United States Pharmacopœia (9th Rev.) gives the following process for the determination of the total alkaloids in jaborandi leaves :

Fifteen grammes of leaves in No. 60 powder are placed in a 250 c.c. flask with 150 c.c. of chloroform, and, after shaking well and allowing to stand for ten minutes, 5 c.c. of ammonia solution are added and the mixture shaken vigorously every ten minutes during two hours. Five cubic centimetres of water are then added, the mixture again shaken and when the drug has settled, 100 c.c. of the chloroformic layer (= 10 grm. of drug) are drawn off, filtered through cotton wool into a separator, a little ether being used to rinse the cotton wool and the measuring vessel. The alkaloids are then extracted from the chloroform by shaking out with weak sulphuric acid and re-extracted from this by making alkaline with ammonia and agitating with chloroform. The solvent is distilled from the combined chloroform extract, the dry residue dissolved in 8 c.c. of

[1] Paul and Cownley, *Pharm. Journ.* 1896 [iv], **3**, 1.
[2] Evans, *Analytical Notes*, 1906, p. 21 ; 1908, p. 20 ; 1909, p. 35.
[3] Jowett and Pyman, *Proc. Chem. Soc.* 1912, **28**, 268.

$N/10$ sulphuric acid, and the excess of acid titrated with $N/50$ potassium hydroxide, using cochineal solution as indicator. Each cubic centimetre of $N/10$ sulphuric acid used is equivalent to 0·0208 grm. of total alkaloids.

Jowett has pointed out [1] that the estimation of the total alkaloids is of little value since *iso*pilocarpine is less active than pilocarpine, and has suggested the following method for the examination of the total alkaloid with a view to obtaining an approximate idea of the amount of pilocarpine present :

The varnish obtained by extracting the total alkaloids by any suitable process is dissolved in a small quantity of a saturated alcoholic solution of pilocarpine nitrate, and to the solution a strong, freshly prepared alcoholic solution of nitric acid is added until the mixture is distinctly acid. A small crystal of pilocarpine nitrate is added and the whole set aside two hours to crystallise. The mixture is vigorously stirred ; any crystals which have separated are filtered off, washed with a saturated alcoholic solution of pilocarpine nitrate, dried and weighed. This may for most purposes be taken as pilocarpine nitrate, but it should be examined by the determination of its melting-point and specific rotation. The former constant should be between 164° and 174°, and from the rotation found the percentage of pilocarpine (p) present may be calculated from the formula $p = 100(n—38·5)/43·7$, where n is the observed specific rotation.

The alkaloids of jaborandi leaves may be prepared as follows : The finely powdered leaves are extracted with alcohol containing 1 per cent. of hydrochloric acid. The solvent is distilled off, the aqueous residue filtered, made just neutral by addition of ammonia, allowed to stand until resin is no longer deposited, and the clear liquid evaporated to a low bulk. Excess of ammonia is then added and the free alkaloids shaken out with chloroform. The latter is distilled off, the residue dissolved in a small volume of water and neutralised by dilute nitric acid. The nitrates which crystallise out are separated into pilocarpine and *iso*pilocarpine nitrates by recrystallisation from alcohol.

Pilocarpine, $C_{11}H_{16}O_2N_2$. Pilocarpine is a colourless oil, b.p. 260°/5 mm. (partially isomerised on distillation), $[\alpha]_D + 100·5°$, freely soluble in water, alcohol, or chloroform, but almost insoluble in ether or light petroleum. The salts with acids crystallise well ; the nitrate, $B.HNO_3$, forms well-defined prisms, m.p. 178°, $[\alpha]_D$

[1] *Year Book of Pharmacy,* 1899, **36,** 435.

$+ 82\cdot9°$, and dissolves in 6·4 parts of water at 20° or 146 parts of alcohol (95 per cent.) at 15°; the hydrochloride, B.HCl, prisms, m.p. 204°–205°, $[\alpha]_D + 91\cdot74°$. The nitrate and hydrochloride are chiefly used in medicine.[1] The hydrobromide forms small prisms, m.p. 185°, $[\alpha]_D + 77\cdot05°$; the aurichloride, $B.HAuCl_4.H_2O$, small lemon-yellow needles, m.p. 117°–130° (*dry*); and the picrate, characteristic long needles, m.p. 147° (Jowett); 159°-160° (Petit and Polonovski).

Pilocarpine dissolves in dilute soda solution, and the rotation is thereby reduced due to the formation of the sodium salt of pilocarpic acid, $C_{11}H_{18}O_3N_2$, of which pilocarpine is the lactone, and, in like manner, amorphous barium and copper salts $(C_{11}H_{15}O_3N_2)_2Cu$, may be prepared.

*iso***Pilocarpine,** $C_{11}H_{16}O_2N_2$ (*Pilocarpidine*, Petit and Polonovski; *β-Pilocarpine*, Bruhl). When pilocarpine is heated alone, or, better, when a solution in alcoholic soda is boiled, it is converted into an isomeride, *iso*pilocarpine. The latter is found in the leaves of *Pilocarpus microphyllus*, and, according to Jowett, may occur in the pilocarpine nitrate of commerce. It is a colourless viscid oil, b.p. 261°/10 mm., $[\alpha]_D + 42\cdot8°$, readily soluble in water, alcohol, or chloroform. It forms crystalline salts with acids; the nitrate crystallises from water in prisms, m.p. 159°, $[\alpha]_D + 35\cdot68°$; the hydrochloride, $(B.HCl)_2.H_2O$, has m.p. 127° or 159° (*dry*), whilst the aurichloride, $B.HAuCl_4$, forms lemon-yellow needles, m.p. 158°–159°. When *iso*pilocarpine is dissolved in water and a molecular proportion of soda added, the rotation is reduced to zero due to the formation of sodium *iso*pilocarpate.

METAPILOCARPINE. According to Pinner this second isomeride is formed when pilocarpine hydrochloride is heated at 225°–235° during one to two hours. It differs from pilocarpine and *iso*pilocarpine chiefly in yielding less soluble salts. In the free state it has the composition $C_{11}H_{18}O_3N_2$, but in its salts it appears to exist as $C_{11}H_{16}O_2N_2$. According to M. and M. Polonovski, the lactone group is absent in metapilocarpine.[2]

Constitution of Pilocarpine and iso*Pilocarpine.* The structure of pilocarpine was first investigated by Hardy and Calmels,[3] who assigned to it a formula which was shown later on by various investigators to be untenable. Our present knowledge of the two alkaloids is mainly due to Jowett.

[1] *Cf.* Jowett, *Pharm. Journ.* 1899, July 29.
[2] *Bull. Soc. chim.* 1922 [iv], **31**, 1204.
[3] *Compt. rend.* 1886, **102**, 1116, 1251, 1562; **103**, 277; 1887, **105**, 68.

On oxidation with permanganate, *isopilocarpine* yields *homopilopic acid*, $C_8H_{12}O_4$ and *pilopic acid*, $C_7H_{10}O_4$.

This mixture of acids is best separated by fractional distillation of the ethyl esters. In this way a large fraction of an ester, $C_9H_{14}O_4$, b.p. 290°–300°, is obtained, which on hydrolysis furnishes pilopic acid, $C_7H_{10}O_4$, crystallising in silky plates, m.p. 104°, $[\alpha]_D + 36\cdot1°$. When pilopic acid is digested in the cold with barium hydroxide a salt of the composition $(C_7H_9O_4)_2Ba$ is formed, but when the acid is boiled with a solution of barium hydroxide for an hour, and the filtrate, after removal of excess of baryta by a current of carbon dioxide, is evaporated and excess of alcohol added, a barium salt of the formula $C_7H_{10}O_5Ba$ is obtained. Pilopic acid is, therefore, a lactonic acid, furnishing on hydration the hydroxy-acid, $C_7H_{12}O_5$. When fused with potash, pilopic acid is converted into *normal* butyric acid. The constitution of pilopic acid is discussed below.

Homopilopic acid, $C_8H_{12}O_4$, obtained by hydrolysis of the higher boiling fraction of ethyl ester, is a viscid colourless oil, b.p. 235°–237°/20 mm., $[\alpha]_D + 45\cdot4°$. With cold baryta water the acid furnishes a microcrystalline barium salt of the formula $(C_8H_{11}O_4)_2Ba$, and with boiling baryta water the salt of the hydroxy-acid $C_8H_{12}O_5Ba$. It is, therefore, also a lactonic acid. When fused with excess of potash it furnishes α-ethyltricarballylic acid, $COOH.CH(C_2H_5).$ $CH(COOH).CH_2.COOH$, which could be formed from any one of the three isomeric hydroxy-acids of the following formulæ :

$$CH_2OH.CH(C_2H_5).CH(COOH).CH_2.COOH$$
$$COOH.CH(C_2H_5).CH(CH_2OH).CH_2.COOH$$
$$COOH.CH(C_2H_5).CH(COOH).CH_2.CH_2OH$$
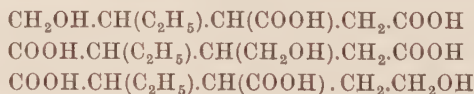
Homopilopic acid is very stable, and is probably therefore the γ-lactonic acid of one of these three hydroxy-acids. Further, pilopic acid seems to be produced from its higher homologue by loss of carbon dioxide and oxidation of the contiguous carbon atom. Of the four γ-lactonic acids derivable from the three hydroxy-acids formulated above only two answer these conditions, viz. :

$$\begin{array}{cc}
CH(C_2H_5).CH.CH_2.COOH & \quad CH(C_2H_5).CH.CH_2.COOH \\
\mid \qquad \mid & \qquad \mid \qquad \mid \\
CH_2-O-CO & \qquad CO-O-\cdot CH_2 \\
\text{(I)} & \qquad \text{(II)}
\end{array}$$
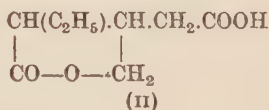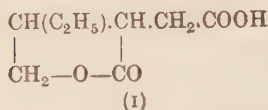
Homopilopic acid (Jowett)

and these lead to the following possible formulæ for pilopic acid :

$$CH(C_2H_5)-CH.COOH$$
$$CH_2-O\underline{\quad}CO$$
(III)

$$CH(C_2H_5)-CH.COOH$$
$$CO-O\underline{\quad}CH_2$$
(IV)
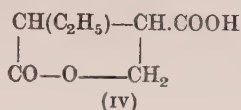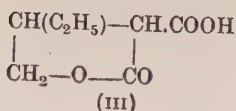
Pilopic acid (Jowett)

A substance having formula III would probably lose carbon dioxide on heating, whereas pilopic acid is stable even at 200°. It is probable, therefore, that homopilopic acid is represented by formula II and pilopic acid by formula IV. Jowett has also shown that pilocarpine, like *iso*pilocarpine, yields homopilopic acid when oxidised by permanganate.[1]

In the oxidation of the two alkaloids the same author has pointed out that the two nitrogen atoms are eliminated as ammonia and methylamine.

From these and other experimental results Pinner and Schwarz [2] suggested that pilocarpine could be represented by formula v, and subsequently Jowett confirmed the validity of this formula to a certain extent by the preparation of a series of disubstituted glyoxalines from *iso*pilocarpine by distillation with soda-lime,[3] although he pointed out that the reactions of the alkaloid were equally well accounted for by formula VI :

$$C_2H_5.CH.CH.CH_2.C.N(CH_3)$$
(v)

$$C_2H_5.CH.CH.CH_2.C\underline{\quad\quad}N$$
(VI)
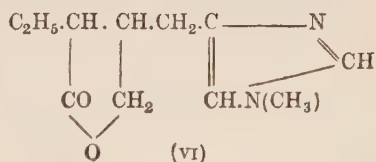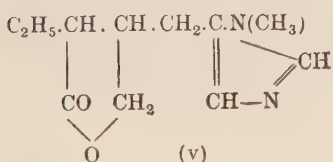
since it was then impossible to decide whether the dialkylglyoxalines produced on distillation with soda-lime are 1 : 4 or 1 : 5 derivatives. Pyman has recently shown that the dimethylglyoxaline so formed is the 1 : 5 derivative, thus supporting formula v.[4] The same author has synthesised a number of bases allied to pilocarpine in constitution.[5]

[1] *Trans. Chem. Soc.* 1903, **83**, 451. *Cf.* Pinner and collaborators, *Berichte*, 1900, **33**, 1424, 2357 ; 1901, **34**, 727 ; 1902, **35**, 204, 2443 ; 1905, **38**, 2560.

[2] *Berichte*, 1902, **35**, 2441.

[3] *Trans. Chem. Soc.* 1903, **83**, 442.

[4] *Ibid.* 1922, **121**, 2616. *Cf.* 1910, **97**, 1820 ; and Polonovski, *Bull. Soc. Chim.* 1922 [iv], **31**, 1204.

[5] *Trans. Chem. Soc.* 1912, **101**, 530.

The relationship existing between pilocarpine and *iso*pilocarpine is at present uncertain ; both alkaloids furnish homopilopic acid when oxidised with permanganate, but with bromine pilocarpine is converted into bromocarpinic acid, $C_{10}H_{15}O_4N_2Br$, whilst *iso*pilocarpine is changed into dibromo*iso*pilocarpinic acid, $C_{11}H_{14}O_4N_2Br_2$, and similarly oxidation with chromic acid leads to the formation of pilocarpoic acid, $C_{11}H_{16}O_5N_2$, in the case of pilocarpine, but with *iso*pilocarpine total disruption of the molecule occurs. In spite of these differences it appears probable that the alkaloids are stereo-isomeric and that in the formation of *iso*pilocarpine from pilocarpine, under the influence of heat alone or by the action of alkali hydroxides, partial racemisation occurs, which would account for the lower specific rotation of the former. In support of this view may also be quoted the facts (1) that the absorption spectra of the nitrates of the two alkaloids are identical, although, as has been pointed out by Hartley,[1] such spectra are merely those of the acid modified by the presence of the alkaloids, and (2) that in the action of alkalis on *iso*pilocarpine or pilocarpine an equilibrium mixture of both alkaloids is formed.[2a] Recent work by M. and M. Polonovski supports these views.[2b]

Pilocarpidine, $C_{10}H_{14}O_2N_2$. This alkaloid was first obtained by Harnack[3] from *Pilocarpus Jaborandi*, and later by Merck from the same source, being found in the mother liquors from crystallisation of pilocarpine nitrate. According to Jowett[4] it does not occur in the leaves of *Pilocarpus microphyllus*. The free base is a viscid oil, $[\alpha]_D + 81\cdot3°$ (less in presence of alkali), miscible with water. The salts crystallise well ; the nitrate, $B\cdot HNO_3$, in colourless prisms, m.p. 137°, $[\alpha]_D + 73\cdot2°$, soluble in water (1 in 2 at 15°). The auri-chloride, unlike that of pilocarpine, is very soluble in water, but crystallises from acetic acid, m.p. 124°–125°. The platinichloride, $(B\cdot HCl)_2PtCl_4\cdot4H_2O$, forms yellow needles, m.p. 187° (*dry*). The picrate, unlike the corresponding salts of pilocarpine and *iso*pilocarpine, is an oil. The base does not contain a : NCH_3 group, and is probably a glyoxaline derivative with a free imino group, since it gives a deep red coloration with sodium diazobenzene sulphonate.

Pilocarpidine reacts with methyl iodide to form a methiodide,

[1] *Proc. Chem. Soc.* 1903, p. 122.

[2] (*a*) Jowett, *Trans. Chem. Soc.* 1905, **87**, 797. *Cf.* Pinner, *Berichte*, 1905, **38**, 1510 ; (*b*) *Bull. Soc. chim.* 1922 [iv], **31**, 1027, 1185, 1201, 1204, 1314.

[3] *Annalen*, 1887, **238**, 230.

[4] *Trans. Chem. Soc.* 1900, **77**, 474. *Cf.* Pyman, *ibid.* 1912, **101**, 2260.

$C_{10}H_{14}O_2N_2.CH_3I$, from which a methochloride platinichloride, $(B.CH_3Cl)_2.PtCl_4$, m.p. 178°, is obtainable. When warmed with caustic potash solution at 200°, pilocarpidine yields dimethylamine. By repeated evaporation with acids, it is said to be converted into jaboridine, $C_{10}H_{12}O_3N_2$, obtained by Parodi from " false jaborandi " (leaves of *Piper reticulatum*).

Pilosine, $C_{16}H_{18}O_3N_2$, obtained by Pyman [1] from mother liquors remaining after the separation of pilocarpine and *iso*pilocarpine, crystallises from alcohol in large colourless plates, m.p. 187°, $[\alpha]_D$ $+ 39.9°$ (in dry alcohol), lævorotatory in alkaline solution, is sparingly soluble in cold, more so in hot water or alcohol, and very sparingly soluble in boiling chloroform, ether, acetone, or benzene. The salts with acids do not crystallise readily ; the sulphate, $B_2.H_2SO_4$, forms clusters of plates, m.p. 194°–195°, $[\alpha]_D + 21°$ in water ; the acid tartrate, $B.H_2C_4H_4O_6$, m.p. 135°–136°, $[\alpha]_D + 24.2°$; the auri-chloride, $B.HAuCl_4$, separates from acetic acid in wedge-shaped plates, m.p. 143°–144°.

Pilosine contains one : NMe but no . OMe group, and behaves as a lactone. When boiled with a mixture of acetic acid and acetic anhydride, a molecule of water is lost with the formation of ANHYDRO-PILOSINE (colourless rods, m.p. 133°–134°, $[\alpha]_D + 66.2°$, from ethyl acetate), yielding salts which are lævorotatory and solutions in alkali that are strongly lævorotatory. Anhydropilosine still contains the lactone group of the parent alkaloid intact. On distillation with potassium hydroxide solution, pilosine loses benzaldehyde and gives a new alkaloid PILOSININE, $C_9H_{12}O_2N_2$, needles or plates, m.p. 78°–79°, b.p. 300°/35 mm., $[\alpha]_D + 14.2°$ falling to $+ 3.1°$ on keeping (in water). The salts with acids are feebly dextrorotatory and solutions in alkali lævorotatory. On the basis of these reactions and their general similarity to pilocarpine and *iso*pilocarpine in physiological action, Pyman assigned the following formulæ to pilosine and pilosinine :

Pilosine

Pilosinine
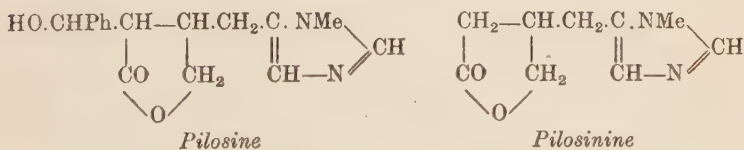
Jaborine, $C_{22}H_{32}O_4N_4$, was obtained by Harnack and Meyer [2]

[1] *Trans. Chem. Soc.* 1912, **101**, 2260.   *Cf.* Léger and Roques, *Compt. rend.* 1912, **155**, 1088 ; 1913, **156**, 1687.
[2] *Annalen*, 1880, **204**, 67.

from the leaves of *Pilocarpus Jaborandi.*   According to Jowett it
is a mixture of pilocarpine, *iso*pilocarpine, and extractive matter.

ψ-**Pilocarpine** and ψ-**Jaborine** were obtained by Petit and Polo-
novsky [1] from *Pilocarpus spicatus* (Aracati jaborandi).   The former
is a colourless syrup giving a nitrate, small needles, m.p. 142°, and
a hydrochloride, prisms, m.p. 198°.   ψ-Jaborine is also amorphous ;
its nitrate forms lamellæ, m.p. 158°, and the hydrochloride needles,
m.p. 222°.   Both are optically inactive.

Physiological Action of Jaborandi Alkaloids.   Pilocarpine causes
increased secretion by the salivary, lachrymal, gastric, and other
glands, the solids of the secretions being increased as well as the
fluids, though to a less extent ; this action is inhibited by atropine,
indicating that pilocarpine acts on the nerve endings in the secretory
cells.   The muscles of a number of organs are contracted after
administration of pilocarpine.   Taken internally or applied locally,
pilocarpine causes contraction of the pupil of the eye.   The heart is
slowed by the alkaloid in general, though in some cases it is accele-
rated and there is a rise in blood-pressure.   The respiratory centre is
not directly affected by small doses, but large doses produce con-
vulsive movements and rapid and laboured respiration, and even-
tually the respiration becomes slow and weak, and asphyxia occurs.
On the whole pilocarpine resembles muscarine in action, but is much
less poisonous.

Pilocarpine is chiefly used in medicine as a diaphoretic in dropsy
and similar diseases.   It has also been employed in ophthalmic
surgery as a substitute for physostigmine to contract the pupil
and reduce the intraocular pressure.   It has been used as an
antidote to atropine, but it does not antagonise the action of atropine
in the central nervous system.

*iso*Pilocarpine and pilocarpidine are stated to have the same
general action as pilocarpine, but are much weaker, pilocarpidine
being the least active of the three.   Pilocarpic acid is inactive.[2]
Pilosine, anhydropilosine and pilosinine, all exhibit a weak pilo-
carpine action.   Jaborine was supposed to exhibit an action similar
to that of atropine, but in view of Jowett's statement that jaborine
is a mixture of pilocarpine and *iso*pilocarpine this statement lacks
confirmation, but it is interesting to note that, according to Schulz,[3]
1-ethyl-2-methylglyoxaline and the 4-chloro derivative of this have,
in some respects, an action resembling that of atropine.

[1] *Chem. Centr.* 1897 [i], 1126.
[2] Marshall, *Journ. Physiol.* 1904, **31**, 123.
[3] *Arch. exp. Path. Pharm.* **13**, 304 ; **16**, 256.

VIII. PURINE GROUP

THIS group includes the important alkaloids occurring in the stimulant foodstuffs, tea, coffee, cocoa, kola, guarana, maté, etc., together with a few others which are found especially in the embryos of leguminous plants. The most important compound of this group occurring in Nature is uric acid, which is employed commercially in some cases for their manufacture, the uric acid being extracted from guano.[1] The alkaloids concerned are as follows :

Caffeine, $C_8H_{10}O_2N_4$, found in tea, coffee, kola, maté and guarana.

Theobromine, $C_7H_8O_2N_4$, found in cocoa.

Theophylline, $C_7H_8O_2N_4$, found in tea.

Xanthine, $C_5H_4O_2N_4$, found in tea.

Hypoxanthine, $C_5H_4ON_4$, found in black pepper.

    Inosine, a pentoside of hypoxanthine, found in yeast and beetroot.

Guanine, $C_5H_5ON_5$, found in guano and leguminous seedlings.

Adenine, $C_5H_5N_5$, found in tea and beetroot.

    Vernine, a pentoside of adenine found in *Vicia* seedlings.

In addition a number of compounds of this class are found in animals, *e.g.*, uric acid, methyl- and dimethyl-xanthines, methyl-guanine, etc., but these do not come within the scope of this volume.

Similarly a number of pyrimidines have been found both in plants and animals, in the former usually in the form of glucosides, of which two, vicine and convicine, are referred to at the end of this section on account of their special interest.

Purine, which may be regarded as the parent of this group of compounds, has been synthesised by E. Fischer,[2] and is repre-

[1] The following are the principal patents taken out since 1900 relating to the preparation of purine derivatives ; the reference in brackets is to the abstract in the *Chemisches Zentralblatt :* German Patents 115,253 (1900 [ii], 1168), 121,224 (1901 [ii], 71), 126,797 (1902 [i], 80), 128,212 (1902 [i], 549), 134,984 (1902 [ii], 1165), 138,444 (1903 [i], 370), 146,714 (1903 [ii], 1484), 146,715 (1903 [ii], 1485), 148,208 (1904 [i], 618), 151,133 (1904 [i], 1430), 161,493 (1905 [ii], 182), 165,561–2 (1906 [i], 300), 166,267 (1906 [i], 618), 222,552 (1910 [ii], 120).

[2] *Berichte*, 1898, **31,** 2550.

sented by formula I, though it may also react in the sense of formula II : [1]

$$
\begin{array}{cc}
\begin{array}{c}
\text{N : CH.C.NH} \\[2pt]
\big| \qquad \| \quad \rangle\text{CH} \\[2pt]
\text{CH : N.C—N}
\end{array}
&
\begin{array}{c}
\text{N : CH.C—N} \\[2pt]
\big| \qquad \| \quad \rangle\text{CH} \\[2pt]
\text{CH : N .C.NH}
\end{array} \\[4pt]
\text{(I)} & \text{(II)}
\end{array}
$$
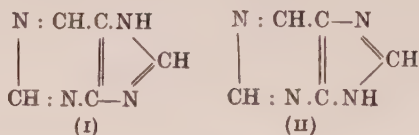
Caffeine (*Theine*), $C_8H_{10}O_2N_4$. This is the principal alkaloidal constituent of tea and coffee, and of the similar stimulant foodstuffs, kola (used throughout West Africa), maté and guarana (both used in South America). It also occurs to a small extent in cocoa beans.[2] The percentages present in these various products are as follows : Tea, 1 to 4·8 ; kola nuts, 2·7 to 3·6 ; coffee, 1 to 1·5 ; maté, 1·25 to 2 ; guarana, 3·1 to 5. It occurs either free or combined as caffeine chlorogenate.[3]

Caffeine is largely prepared from waste tea or tea-dust by extracting this with boiling water, treating the decoction with litharge, and concentrating the filtrate until crystallisation occurs, the caffeine being recrystallised from boiling water.

The following processes for the estimation of the total alkaloids in tea, coffee, and kola are available :

Tea and Coffee. The following modification of Stahlschmidt's process is recommended by Allen.[4] Six grammes of tea (or 12 grm. of coffee) in fine powder are boiled with 500 c.c. of water for six hours under a reflux condenser, the extract filtered off, diluted with water to 600 c.c., heated to boiling and colouring matter removed by adding 4 grm. of lead acetate in powder and stirring well. Five hundred cubic centimetres of the filtrate are collected, concentrated to 50 c.c. and the excess of lead precipitated with sodium phosphate. The filtrate and washings from this are evaporated to 40 c.c., and the caffeine extracted by shaking with successive portions of chloroform until no more alkaloid is removed. The combined chloroform solutions are collected in a tared flask and the residue left on evaporating off the solvent dried and weighed. Its weight represents the amount of alkaloid present in 5 grm. of tea or 10 grm. of coffee.

[1] *Berichte*, 1899, **32**, 435.
[2] Schmidt, *Annalen*, 1883, **217**, 306.
[3] Gorter, *ibid.* 1908, **358**, 327.
[4] *Commercial Organic Analysis*, vol. vi. p. 607. *Cf.* vol. ix. p. 526, for a critical *résumé* of methods. For a useful general method *see* Power and Chesnut, *Journ. Amer. Chem. Soc.* 1919, **41**, 1298.

Kola Nuts. Dieterich gives the following process [1] for the estimation of the total alkaloids (caffeine and theobromine). Ten grammes of the finely powdered drug are mixed with 10 grm. of quicklime and the mixture extracted in a Soxhlet apparatus with chloroform, the solvent distilled off for the most part, the residue warmed with 20 c.c. *N*-hydrochloric acid and the acid solution filtered, the flask and the filter being washed, and the washings added to the filtrate previously placed in a separator. The liquid is now made alkaline with ammonia solution and then extracted three times with chloroform, using 20 c.c. each time. The chloroform is evaporated from the combined extracts and the residue dried till of constant weight.

Caffeine crystallises with one mol. of water from hot water, or anhydrous from alcohol, in slender, silky needles; it becomes anhydrous at 100°,[2] melts at 234°–235° (*dry*), and sublimes at 176°. At 25° one part of caffeine dissolves in the following quantities of the solvents named: Water, 45·6; alcohol, 53·2; ether, 375; chloroform, 8. One part of caffeine is dissolved at the boiling point by the following quantities of the solvents named: Ether, 339; acetic ether, 23·9; benzene, 18·9; chloroform, 6·4. The alkaloid is bitter to the taste. It is a weak base, neutral to litmus, and furnishes salts that are decomposed when their aqueous solutions are evaporated. The double salts are more stable; the mercurichloride, $B.HgCl_2$, forms colourless needles, m.p. 246°, and the aurichloride, $B.HAuCl_4.2H_2O$, golden-yellow leaflets, m.p. 243° or 248·5° (*dry*). When warmed with water the aurichloride loses 2HCl and forms aurichlorcaffeine, $C_8H_9(AuCl_2)O_2N_4$, as a yellow amorphous precipitate.[3] " Caffeine citrate," the form in which the alkaloid is principally used in medicine, is prepared by evaporating to dryness a solution of equal weights of caffeine and citric acid in water. It is a colourless powder which dissolves unchanged in a little water, deposits caffeine on dilution, the solution becoming clear on further addition of water. The solubility of caffeine in water is increased by the presence of lithium benzoate, sodium metaphosphate, salicylate, or benzoate, potassium bromide and other salts, and combinations such as caffeine sodio-salicylate and caffeine sodio-benzoate, prepared by dissolving caffeine in such solutions and evaporating to dryness, are used in medicine. Caffeine forms similar compounds with salicylic and

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[1] *Pharm. Zeit.* 1897, No. 8.
[2] *Cf.* Tassilly, *Bull. Soc. chim.* 1897 [iii], **17**, 596.
[3] Dunstan and Shepheard, *Trans. Chem. Soc.* 1893, **63**, 198.

gallic acids.[1] The alkaloid also forms additive compounds with pyrogallol and phloroglucinol.[2]

Caffeine dissolves in sulphuric acid, forming a colourless solution, but if a crystal of potassium dichromate is added the solution becomes yellowish-green and finally green. In common with uric acid and all the alkaloids of this group it gives the murexide test, *i.e.*, if a small quantity of the alkaloid is evaporated to dryness with nitric acid, or with hydrochloric acid and potassium chlorate, on the water-bath, the residue gives with ammonia a rich purple colour that is destroyed by the addition of fixed alkalis. Caffeine is not precipitated by Mayer's reagent, but gives a colourless precipitate, soluble in excess, with a solution of tannin.

Constitution. The relationship of caffeine to theobromine and theophylline and to xanthine (*see* p. 333) is shown by its formation from derivatives of these substances. When theobromine is heated with methyl iodide, potassium hydroxide and alcohol, it undergoes methylation, and caffeine is formed. Similarly the silver derivative of theophylline, when warmed with methyl iodide, yields caffeine. Further, when the silver derivative of methylxanthine is treated with methyl iodide, caffeine is produced. The relationship of these four alkaloids is therefore as follows :

Xanthine, $C_5H_4O_2N_4$.

Theophylline, $C_7H_8O_2N_4$ (dimethylxanthine).

Theobromine, $C_7H_8O_2N_4$ (dimethylxanthine).

Caffeine, $C_8H_{10}O_2N_4$ (trimethylxanthine).

A method for the conversion of caffeine into theophylline and xanthine has been described by Fischer and Ach.[3]

Numerous syntheses of caffeine have been described beginning with that of Fischer and Ach.[4]

The following method is due to Traube.[5] Carbamide treated with cyanoacetic acid in presence of phosphorus oxychloride yielded cyanoacetylcarbamide (I), and this treated with sodium hydroxide, followed by acetic acid, gave 4-amino-2 : 6-dioxypyrimidine (II). The latter furnished an oximino-derivative, which on reduction yielded 4 : 5-diamino-2 : 6-dioxypyrimidine (III), and this as an

[1] Brissemoret, *Bull. Soc. chim.* 1906 [iii], **35**, 316.

[2] Ultée, *Chem. Weekbl.* 1910, **7**, 32.

[3] *Berichte*, 1906, **39**, 423.

[4] *Ibid.* 1895, **28**, 3135.

[5] *Ibid.* 1900, **33**, 1371, 3035.

o-diamine condensed with formic acid to yield a formyl derivative (IV) which on heating at 100°–220° yielded xanthine (V).

$$
\begin{array}{ccc}
\text{NH--CO} & \text{NH--CO} & \text{NH--CO} \\
|\quad\quad| & |\;^1\;^6| & |\quad\quad| \\
\text{CO}\quad\text{CH}_2 & \text{CO}^2\;^5\text{CH}_2 & \text{CO}\quad\text{C.NH}_2 \\
|\quad\quad| & |\;_3\;_4| & |\quad\quad\| \\
\text{NH}_2\;\text{CN} & \text{NH--C : NH} & \text{NH--C.NH}_2 \\
\text{(I)} & \text{(II)} & \text{(III)}
\end{array}
$$

$$
\begin{array}{cc}
\text{NH--CO} & \text{NH--CO} \\
|\quad\quad| & |\quad\quad| \\
\text{CO}\quad\text{C.NH.CHO} & \text{CO}\quad\text{C.NH} \\
|\quad\quad\| & |\quad\quad| \\
 & \quad\quad\;\text{CH} \\
|\quad\quad\| & |\quad\quad\| \\
\text{NH--C.NH}_2 & \text{NH--C.N} \\
\text{(IV)} & \text{(V)}
\end{array}
$$
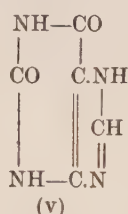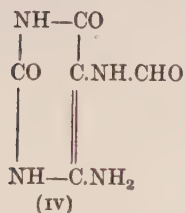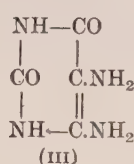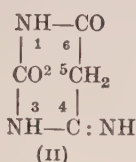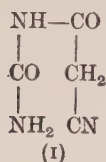
By a precisely similar series of reactions starting from dimethyl-carbamide, Traube obtained theophylline (1 : 3-dimethylxanthine), and this on methylation yielded caffeine (1 : 3 : 7-trimethylxanthine or 1 : 3 : 7-trimethyl-2 : 6-dioxypurine) thus :

$$
\begin{array}{ccc}
\text{CH}_3.\text{N--CO} & \text{CH}_3.\text{N--CO} & \text{CH}_3.\text{N--CO} \\
|\quad\quad| & |\quad\quad| & |\quad\quad| \\
\text{CO}\quad\text{CH}_2 & \text{CO}\quad\text{CH}_2 & \text{CO}\quad\text{C.NH}_2 \\
|\quad\quad| & |\quad\quad| & |\quad\quad\| \\
\text{CH}_3.\text{NH}\;\text{CN} & \text{CH}_3.\text{N--C : NH} & \text{CH}_3.\text{N--C.NH}_2 \\
\text{(I)} & \text{(II)} & \text{(III)}
\end{array}
$$

$$
\begin{array}{ccc}
\text{CH}_3\text{N--CO} & \text{CH}_3.\text{N----CO} & \text{CH}_3.\text{N----CO} \\
|\quad\quad| & |\;^1\;^6| & |\quad\quad| \\
\text{CO}\quad\text{C.NH.CHO} & \text{CO}\quad\text{C--NH} & \text{CO}\quad\text{C--N(CH}_3) \\
|\quad\quad\| & |\;^5\|\;^7\rangle\text{CH} & |\quad\quad\|\rangle\text{CH} \\
\text{CH}_3.\text{N--C.NH}_2 & \text{CH}_3.\text{N----C--N} & \text{CH}_3.\text{N----C--N} \\
\text{(IV)} & \text{(V)} & \textit{Caffeine}
\end{array}
$$
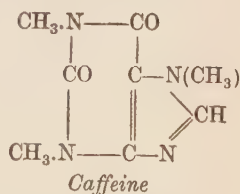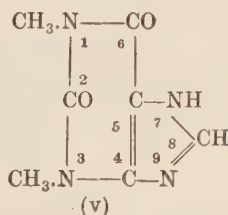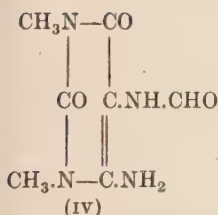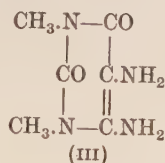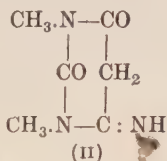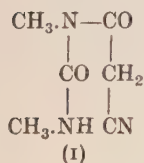
Theobromine, $C_7H_8O_2N_4$, is the chief alkaloid in cocoa beans, but is also found in small quantities in kola nuts and leaves [1] and in tea leaves. For the preparation of theobromine the ground beans are extracted with light petroleum to remove fat, the residue of fat-free beans is made into a paste with lime and extracted with 80 per cent. alcohol until exhausted of alkaloid. For the estimation

[1] Dekker, *Rec. Trav. chim.* 1903, **22**, 143.

of the total alkaloids of cocoa beans the following process, due to Dekker,[1] is available.

Ten grammes of powdered cocoa-beans are mixed with 5 grm. of magnesia and boiled under a reflux apparatus during one hour with 300 c.c. of water. The decoction is filtered off, the residue again boiled with water during fifteen minutes and the second decoction filtered. The combined filtrates are evaporated to dryness on the water-bath, the residue mixed with sand and extracted in a Soxhlet apparatus with chloroform. The solvent is distilled off and the residue dried and weighed. The quantity of total alkaloid in cocoa beans varies from 1·2 to 2·2 per cent., whilst the husks contain about 0·5 per cent. About half the theobromine appears to be present in a free state.

The recorded results show much greater variation than this, probably due to the use of methods of estimation which do not remove the whole of the theobromine. It is stated that caffeine may be fairly completely separated from theobromine by extraction with cold benzene in which theobromine is practically insoluble.

Theobromine forms microscopic crystals belonging to the rhombic system, melts at 329°–330° in a closed capillary tube, sublimes at 290°–295°, and is sparingly soluble in most solvents. One part of theobromine is soluble in the following quantities of the solvents named at 15° : Water 1,800, dry alcohol 3,570, chloroform 3,845, ether 25,000, ethyl acetate 3,845, benzene 100,000.[2] At their boiling points 1 grm. of the alkaloid is dissolved by the following quantities of solvent : ether 3,125, carbon tetrachloride 4,703,[3] chloroform 100,[4] water 150. It is a weak base, neutral to litmus. The salts are decomposed more or less completely by water and in some cases by alcohol. The hydrochloride, $B.HCl.H_2O$, is crystalline, and yields the free base when dried at 100°. The platinichloride, $B_2.H_2PtCl_6.4H_2O$, forms golden-yellow monoclinic prisms. Theobromine forms a series of metallic derivatives of which the most characteristic is silver-theobromine, $AgC_7H_7O_2N_4$, obtained by arming a solution of the alkaloid in ammonia with silver nitrate. Sodium-theobromine is also of considerable importance, since it forms very soluble compounds with sodium chloride and with sodium salts of organic acids, e.g., sodium acetate, formate, benzoate, or salicylate,

---

[1] *Loc. cit.* and *Rev. Intern. Falsif.* 1903, **48**, 36.

[2] Dekker, *Sch. Woch. Pharm.* 1902, **40**, 436.

[3] Göckel, *Chem. Zeit.* 1897, p. 402. *Cf.* Wadsworth, *Analyst*, 1920, **45**, 133.

[4] Dekker, *loc. cit.*

and such compounds are used in medicine (*see* p. 340), as well as similar double salts containing lithium, since they are usually more soluble than theobromine.

Theobromine, like caffeine, gives the murexide test (p. 332) : it is not precipitated by iodine solution or by Mayer's reagent.

Constitution. Theobromine has been synthesised by Fischer [1] and by Traube.[2] The latter utilised a series of reactions parallel with that described on p. 332, starting with methylcarbamide as a raw material, which furnishes as an end-product 3-methyl-xanthine (v) :

$$
\begin{array}{ccc}
\mathrm{NH-CO} & \mathrm{NH-CO} & \mathrm{NH-CO} \\
| \quad | & | \quad | & | \quad | \\
\mathrm{CO \quad CH_2} \rightarrow & \mathrm{CO \quad CH_2} \rightarrow & \mathrm{CO \quad C.NH_2} \rightarrow \\
| \quad | & | \quad | & | \quad \| \\
\mathrm{CH_3.NH \quad CN} & \mathrm{CH_3N - C:NH} & \mathrm{CH_3N - C.NH_2}
\end{array}
$$

$$
\begin{array}{cc}
\mathrm{NH-CO} & \mathrm{NH-CO} \\
| \quad | & | \quad | \\
\mathrm{CO \quad C.NH.CHO} \longrightarrow & \mathrm{CO \quad C-NH} \\
| \quad \| & | \quad \| \quad * \diagdown \mathrm{CH} \\
\mathrm{CH_3N - C.NH_2} & \mathrm{CH_3.N - C - N \diagup}
\end{array}
$$

(v)

3-Methylxanthine on treatment with methyl iodide and alkali undergoes methylation at the point marked * (formula v), yielding 3 : 7-dimethylxanthine identical with natural theobromine.

Theophylline (*Theocine*), $C_7H_8O_2N_4$. This isomeride of theobromine occurs in small quantities in tea, and was obtained therefrom by Kossel [3] by the following process. An alcoholic extract of tea was concentrated to a syrup and set aside until caffeine ceased to crystallise out. The filtrate from this was diluted with water, acidified with dilute sulphuric acid, set aside for some hours and then filtered. The filtrate was made alkaline with ammonia solution, silver nitrate solution added, and the mixture allowed to stand during twenty-four hours. The precipitate was then collected and dissolved in warm diluted nitric acid. On cooling, silver-adenine and silver-hypoxanthine crystallised out. From the filtrate, ammonia precipitated silver-theophylline, which was collected, suspended in water and decomposed by hydrogen sulphide. On concentrating the filtrate, xanthine and finally theophylline crystallised out.

[1] *Berichte*, 1897, **30**, 1845.
[2] *Ibid.* 1900, **33**, 3035.
[3] *Zeits. physiol. Chem.* 1889, **13**, 298.

More theophylline was obtained from the mother liquor by precipitating it with mercuric nitrate and decomposing the mercury-precipitate with hydrogen sulphide. The theophylline used in medicine is produced synthetically.

Theophylline crystallises, with $1H_2O$, in thin monoclinic tablets or needles (from hot water), melts at $264°$, is sparingly soluble in cold, but readily in hot water. It is a weak base, neutral to litmus, and yields salts with acids, as well as derivatives with metals. The hydrochloride, $B.HCl.H_2O$, loses all its water and acid at $100°$. The aurichloride forms lemon-yellow needles. Theophylline gives the murexide reaction (p. 332) and in general resembles theobromine ; thus it furnishes soluble double salts with organic sodium salts, and one of these, sodium-theophylline-sodium acetate, as well as theophylline itself, has been used in medicine.

Constitution. Theophylline has been synthesised by Fischer and Ach [1] and by Traube,[2] whose method has been described already (p. 332) in connection with the synthesis of caffeine. It is 1 : 3-dimethylxanthine (1 : 3-dimethyl-2 : 6-dioxypurine).

Hypoxanthine (*Sarcine*), $C_5H_4ON_4$, is widely distributed both in animals and plants. Among the latter it occurs in mustard, black pepper, melon, barley, and other seeds, as well as in potatoes, yeast, beetroot, and in lupin and other seedlings. According to Kruger it does not occur in tea.[3] Probably in all cases it is a decomposition product of nucleins. Its isolation has been described already (*see* p. 335).

It forms microscopic needles, decomposes at $150°$, and is sparingly soluble in cold water (1 in 1,400 at $19°$), more so in hot water (1 in $69·5°$ at $100°$), readily in acids or alkalis. It is a weak monoacidic base and, like other alkaloids of this group, forms metallic derivatives. Its constitution is determined by the fact that it is formed from adenine (6-aminopurine) by the action of nitrous acid.[4]

Adenine (6-aminopurine)   Hypoxanthine (6-oxypurine)
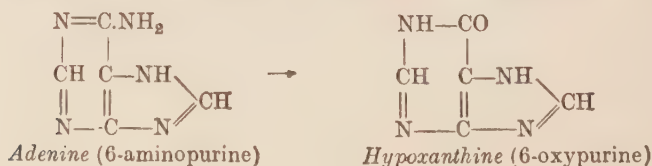
[1] *Berichte*, 1895, **28**, 3135.
[2] *Ibid.* 1900, **33**, 3035.
[3] *Chem. Soc. Abstr.* 1896 [i], 450.   *Cf.* Kossel, *loc. cit.*
[4] *Cf.* Fischer, *Berichte*, 1897, **30**, 555, 2228 ; Traube, *Annalen*, 1904, **331**, 64.

INOSINE, $C_{10}H_{12}O_5N_4$. The carnine which occurs in meat extract and also in yeast and beetroot (Lippmann), has been shown by Haiser and Wenzel [1] to be a molecular mixture of hypoxanthine (*see* p. 336) and inosine. The latter can be separated by washing carnine repeatedly with water or by treating it with acetic anhydride and sodium acetate. In the latter case inosine is obtained as the acetate, glistening needles or plates, m.p. 236° (*decomp.*). Inosine itself forms slender silky needles, m.p. 215° (*decomp.*), $[\alpha]_D^{18} - 49\cdot2°$, sparingly soluble in water (1·615 in 100 at 20°). It is hydrolysed by dilute sulphuric acid into hypoxanthine and *d*-ribose, m.p. 86°–87°, the osazone of which melts at 163°.

Xanthine, $C_5H_4O_2N_4$, occurs somewhat commonly in the animal organism, but is also found in small quantities in yeast, beetroot, lupin and *Vicia* seedlings, and in tea. Its isolation from tea has been described under theophylline (p. 335).

Xanthine crystallises in microscopic, glancing plates (with $1H_2O$) when a dilute warm alkaline solution is acidified with acetic acid and allowed to cool slowly. It becomes anhydrous at 125°–130°, is sparingly soluble in cold water (1 in 14,151 at 16°), rather more soluble in hot water (1 in 1,500 at 100°), and readily soluble in alkalis or acids. A process for its identification has been given by Fischer. [2] It is a very weak base, yielding unstable salts with acids and derivatives with metals. It gives the murexide reaction (*see* p. 332). Xanthine has been synthesised by Fischer [3] and also by Traube (*see* p. 332), and shown to be 2 : 6-dioxypurine.

Guanine, $C_5H_5ON_5$, occurs commonly in animal organisms, and has also been found in small quantities in yeast, sugar-cane, and in beetroot, [4] but is usually prepared from guano. [5] It is a white crystalline powder, insoluble in water and very sparingly soluble in ammonia. It has been synthesised by Fischer [6] and also by Traube. [7] It is 2-amino-6-oxypurine, as shown by the formation from it of xanthine (*see above*) by the action of nitrous acid, or by boiling with hydrochloric acid. [8]

[1] *Monats.* 1908, **29**, 157 ; 1909, **30**, 147, 377 ; 1910, **31**, 357. *Cf.* Levene and Jacobs, *Berichte*, 1909, **42**, 335, 1198, 2102, 3247 ; Neuberg and Brahn, *Biochem. Zeits.* 1909, **17**, 293.

[2] *Berichte*, 1898, **31**, 2550.

[3] *Ibid.* 1897, **30**, 2232.

[4] Lippmann, *ibid.* 1896, **29**, 2653.

[5] Strecker, *Annalen*, 1861, **118**, 152.

[6] *Berichte*, 1897, **30**, 553, 2226.

[7] *Ibid.* 1900, **33**, 1378.

[8] Fischer, *ibid.* 1910, **43**, 805.

$$\begin{array}{c}
\text{HN—CO} \\
|\quad | \\
\text{NH}_2.\text{C}\quad\text{C—NH} \\
\|\quad\|\qquad\diagdown\text{CH} \\
\text{N—C——N}\diagup
\end{array}
\qquad\longrightarrow\qquad
\begin{array}{c}
\text{HN—CO} \\
|\quad | \\
\text{CO}\quad\text{C—NH} \\
|\quad\|\qquad\diagdown\text{CH} \\
\text{NH—C——N}\diagup
\end{array}$$

<div align="center">Guanine   Xanthine</div>

VERNINE, $C_{10}H_{13}O_5N_5.2H_2O$, was obtained by Schulze and his collaborators [1] from lupin seeds and from the embryos of *Vicia sativa*, *Trifolium pratense*, and other plants, and by Lippmann from beet-root residues. It crystallises in small prisms, $[\alpha]_D^{20} - 60°$ in alkali, is readily soluble in hot water, but sparingly so in cold water. It forms amorphous compounds with mercuric and silver nitrates, and when boiled with hydrochloric acid furnishes guanine, and a pentose, probably d-ribose. According to Schulze and Trier,[2] Levene and Jacobs' guanosine [3] is identical with vernine.

A second guanine pentoside has been found by Andrlik [4] in molasses, but Schulze and Trier have shown [5] that this is identical with vernine (guanine-d-ribose).

Adenine, $C_5H_5N_5$, occurs in the pancreas and in small quantities in yeast, tea, beetroot, chayote fruit and bamboo shoots. It crystallises with 3 mols. of water in long colourless needles, sublimes at 220°, softens at 250°, and melts at 360°–365°. It is sparingly soluble in cold but easily in hot water. Adenine picrolonate, m.p. 265°, crystallises from water. The base was synthesised by Fischer [6] by treating trichloropurine (I) with aqueous ammonia, which produced 6-amino-2 : 8-dichloropurine (II), and this on reduction with hydriodic acid yielded adenine (III), thus :

$$\begin{array}{c}
\text{N}\!=\!\text{CCl} \\
|\quad | \\
\text{C.Cl}\quad\text{C—NH} \\
\|\quad\|\qquad\diagdown\text{C.Cl} \\
\text{N—C——N}\diagup
\end{array}
\;\longrightarrow\;
\begin{array}{c}
\text{N}\!=\!\text{C.NH}_2 \\
|\quad | \\
\text{C.Cl}\quad\text{C—NH} \\
\|\quad\|\qquad\diagdown\text{CCl} \\
\text{N—C——N}\diagup
\end{array}
\;\longrightarrow\;
\begin{array}{c}
\text{N}\!=\!\text{C.NH}_2 \\
|\quad | \\
\text{CH}\quad\text{C—NH} \\
\|\quad\|\qquad\diagdown\text{CH} \\
\text{N—C——N}\diagup
\end{array}$$

<div align="center">
2 . 6 · 8-Trichloropurine   6-Amino-2 : 8-dichloropurine   Adenine (6-amino-
(I)   (II)   purine)
                                            (III)
</div>
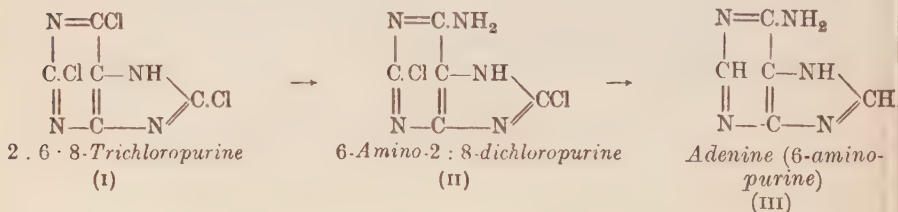
A synthesis of adenine has also been effected by Traube by the

[1] *Zeits. Physiol. Chem.* 1885, **9,** 420 ; 1886, **10,** 326 ; 1904, **41,** 455 ; 1910, **66,** 128.

[2] *Ibid.* 1910, **70,** 143.

[3] *Berichte,* 1909, **42,** 2469.

[4] *7th Int. Congr. Appl. Chem.* 1909, Sect. V, 331.

[5] *Zeits. physiol. Chem.* 1912, **76,** 145.

[6] *Berichte,* 1897, **30,** 2226.

general method already described (p. 332), using thiocarbamide and malononitrile, the thioadenine formed being oxidised to adenine by hydrogen peroxide.[1]

Vicine, $C_{10}H_{16}O_8N_4$ or $C_{10}H_{16}O_7N_4$ (Winterstein), has been obtained together with convicine from various species of vetch, *e.g.*, *Vicia sativa*, *V. Faba*, and *V. Faba minor*.[2] It crystallises in voluminous masses of white needles, becomes anhydrous at 120°, and melts at 242°, $[\alpha]_D^{25} - 11\cdot7°$ or $-8\cdot7°$ in dilute sulphuric acid, $-12\cdot1°$ in $N/5$ sodium hydroxide ; it dissolves in water or methyl alcohol, but is insoluble in dry ethyl alcohol. The sulphate, $B_3 . 4H_2SO_4$, and the hydrochloride, $B_4 . 11HCl$, separate in fine white needles from their aqueous solutions on addition of alcohol.

Boiling dilute sulphuric acid hydrolyses vicine, forming dextrose and divicine, $C_4H_6O_2N_4$, which has been shown to be 2 : 5-diamino-tetrahydropyrimid-4 : 6-dione, so that vicine is regarded as a mono-nucleoside composed of this substance and dextrose.[3] Vicine and its decomposition products dissolve in acids producing yellow colours, and the solutions after warming give with ferric chloride and ammonia a deep blue colour, changing into violet on addition of barium hydroxide.

Convicine, $C_{20}H_{28}O_{16}N_6 . 2H_2O$, occurs with vicine in *Vicia* species (*see above*). It forms thin glancing leaflets, dissolves in boiling water, but is insoluble in cold water or alcohol.[4] It gives the murexide reaction, and on heating with dilute sulphuric acid yields alloxantine, ammonia, and a hexose.[5]

Physiological Action of the Purine Bases. Foodstuffs containing caffeine and theobromine with smaller quantities of the other naturally occurring xanthine bases are used in many parts of the world as stimulants. The use of tea, coffee, and cocoa among civilised peoples is well known, but there are a number of other similar products in use by uncivilised peoples. Kola nuts are used in this way by natives throughout West Africa, guarana by natives in the Argentine, and maté by Indians in Brazil, whilst the Arabs used not

[1] *Annalen,* 1904, **331**, 64.

[2] Ritthausen, *Journ. prakt. Chem.* 1870 [ii], **1**, 336 ; 1873 [ii], **7**, 374 ; 1881 [ii], **24**, 202 ; 1884 [ii], **29**, 359 ; 1899 [ii], **59**, 480. *Cf.* Schulze and Trier, *Zeits. physiol. Chem.* 1910, **70**, 143.

[3] Johnson, *Journ. Amer. Chem. Soc.* 1914, **36**, 337, 545 ; Levene, *J. Biol. Chem.* 1914, **18**, 305 ; 1916, **25**, 607 ; Fischer, *Berichte*, 1914, **47**, 2611 ; Winterstein, *Zeits. physiol. Chem.* 1919, **105**, 258.

[4] Ritthausen, *J. prakt. Chem.*, 1881 [ii], **24**, 212 ; 1899 [ii], **59**, 487.

[5] Schulze and Trier, *Zeits. physiol. Chem.*, 1910, **70**, 143. *Cf.* Johnson, *Journ. Amer. Chem. Soc.* 1914, **36**, 337.

only coffee but also the flowers of *Catha edulis*, which are believed to contain an alkaloid of this group.

The alkaloids chiefly concerned are caffeine, theobromine, and theophylline, although in recent years a very large number of xanthine derivatives have been prepared synthetically, some of which have been, or are being used in medicine.

Caffeine stimulates the central nervous system, especially the part associated with psychical functions, and increases the capacity for physical exertion. In large doses it may cause headache, and in specially susceptible people mild delirium. Theophylline resembles caffeine in its action on the central nervous system, but theobromine is less active in this respect. In small amounts caffeine increases the irritability of muscle, as well as its strength and extensibility, and some investigators attribute the increased capacity for work induced by caffeine to this direct action. Theobromine exerts a greater action on muscle than caffeine, and xanthine is still more active.

Caffeine also stimulates the vaso-motor centre in the medulla and the heart, causes a rise in blood-pressure, and accelerates and strengthens the respiration.

The most important physiological action of caffeine and the related bases is, however, that on the kidney, since they cause increased secretion of urine. The mechanism of this action is still a matter of dispute, but it is generally regarded as due to direct action on the renal cells. Theophylline appears to be the most active of the naturally occurring xanthine bases in this respect.

Caffeine is excreted in the urine, partly unchanged, but chiefly as dimethylxanthine, methylxanthine and xanthine. Theobromine and theophylline are excreted as methylxanthines.[1]

One of the difficulties experienced in the use of these alkaloids in medicine is their insolubility. To overcome this the soluble double salts formed with various sodium salts have been utilised, and several of these are now in use, *e.g.*, diuretine (sodium-theo-bromine-sodium salicylate), agurine (sodium-theobromine-sodium acetate) uropherine (lithium diuretine), uropherine-β (theobromine-lithium benzoate), barutine (barium-theobromine-sodium salicylate), and theocine sodium acetate (sodium-theophylline-sodium acetate). Among the soluble compounds of this kind described in recent years are caffeine-aminoaceto-*p*-phenetidide,[2] combinations of caffeine,

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[1] *Cf.* Levinthal, *Zeits. physiol. Chem.* 1912, **77,** 259.
[2] German Patent 244,740 (*Chem. Soc. Abstr.* 1912 [i], 580).

theobromine and theophylline with sodium 2-methylquinoline-6-carboxylate,[1] acylsalicyl derivatives of theobromine,[2] dialkylaminoethyl derivatives of theobromine [3] and compounds of mono- and dialkyl-xanthines with aliphatic carboxylic acids.[4]   The combination of phenacyl and dihydroxyphenacyl groups with the xanthines failed to eliminate the nerve-stimulating action and retain the cardiac action of the alkaloids.[5]

Much more interesting from a general point of view than any of these is the synthesis of glucosides of the xanthine bases by Fischer and his collaborators.[6]   These are for the most part soluble in water and retain the characteristic action of the alkaloids.

ALKALOIDS OF *SYMPHYTUM OFFICINALE*

From this plant Greimer [7] obtained two poisonous alkaloids, *consolidine* and *symphytocynoglossine*, both of which exerted a paralysing action on the central nervous system.   From the rhizome, Titherley and Coppin have obtained allantoin, $C_4H_6O_3N_4$, which has also been found in a number of other plants, *e.g.*, shoots of the plane tree (*Platanus orientalis*),[8] horse-chestnut (*Æsculus Hippocastanum*),[9] beetroot,[10] peas, and French beans,[11] tobacco seeds,[12] *Datura Metel* seeds.[13]   Its occurrence to the extent of 0·67 per cent. in *Symphytum officinale* [14] is of interest since Macalister and Bramwell have shown [15] that to its remedial action is due the use of this rhizome as a remedy for sores and ulcers.   Allantoin crystallises in needles, m.p. 227°,

[1] German Patent 264,389 (*Chem. Soc. Abstr.* 1914 [i], 80).

[2] German Patent 290,205 (*Chem. Soc. Abstr.* 1916 [i], 500).   *Cf.* German Patent 290,910 (*Chem. Soc. Abstr. ibid.* p. 571) ; Abelin (*Chem. Soc. Abstr.* 1920 [i], 327) ; and German Patent 252,641, *Chem. Soc. Abstr.* 1913 [i], 89).

[3] British Patent 155,748 (*Chem. Soc. Abstr.* 1921 [i], 126).

[4] German Patent 352,980 (*Chem. Soc. Abstr.* 1922 [i], 1071).

[5] Mannich and Kroll, *Ber. deut. Pharm. Ges.* 1921, **31**, 291.

[6] *Berichte*, 1914, **47**, 210, 1058, 3193 ; Helferich and Kühlewein, *ibid.* 1920, **53**, 17, 873.

[7] *Arch. Pharm.* 1900, **238**, 505.

[8] Schulze and Barbieri, *Journ. prakt. Chem.* 1882 [ii], **25**, 147.

[9] Schulze and Booshard, *Zeits. physiol. Chem.* 1892, **9**, 425.

[10] von Lippmann, *Berichte*, 1896, **29**, 2652.

[11] Ackroyd, *Biochem. Journ.* 1911, **5**, 403.

[12] Scurti and Perciabosco, *Gazzetta*, 1906, **36**, 626.

[13] de Plato, *Chem. Soc. Abstr.* 1910 [ii], 742.

[14] Titherley and Coppin, *Pharm. Journ.* 1912 [iv], **34**, 92.   For other cases *see* Steiger, *Zeits. physiol. Chem.* 1912, **86**, 245.

[15] *Brit. Med. Journ.* 1912, **1**, 10, 12.

from boiling water. On hydrolysis by alkalis it furnishes ammonia and carbamide, and on treatment with cold potassium hydroxide solution, yields allantoic acid.[1] Allantoin is a monoureide of the following formula : [2]

$$NH_2.CO.NH.CH\begin{matrix} NH-CO \\ | \\ CO-NH \end{matrix} \qquad (NH_2.CO.NH)_2CH.CO_2H$$

Allantoin   *Allantoic acid*
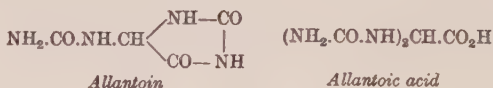
and has been frequently synthesised, *e.g.*, by Grimaux,[3] by condensing carbamide with glyoxylic acid, and by Michael [4] by the action of mesoxalic acid on carbamide.

[1] Behrend and Schultz, *Annalen*, 1909, **365**, 36.
[2] *Cf.* Mendel and Dakin, *J. Biol. Chem.* 1910, **7**, 153 ; Biltz, *Berichte*, 1910, **43**, 1999 ; 1921, **54**, 2451 ; Titherley, *Trans. Chem. Soc.* 1913, **103**, 1336 ; Dakin, *ibid.* 1915, **107**, 434.
[3] *Ann. Chim. Phys.* 1877 [v], **11**, 389. *Cf.* Simon and Chavanne, *compt. rend.* 1906, **143**, 51.
[4] *Amer. Chem. Journ.* 1883, **5**, 198.

IX. ALKALOIDS DERIVED FROM ALIPHATIC AMINES

In other sections of this book reference has been made to the association with alkaloids in plants of comparatively simple amines and amino-acids. Some of these substances, *e.g.*, acetylcholine and *iso*amylamine are physiologically active, and there would be some justification for dealing fully with them in a work on plant alkaloids, and this also applies to such substances as arginine, choline, betaine, and other compounds of this type, but they are much better dealt with as part of the large class of simple basic constituents of plants and animals. An exception has been made in the case of galegine, which was at first erroneously described as a pyrrolidine derivative, but, apart from this, attention will be restricted to a few relatively complex products of this class.

Galegine, $C_6H_{13}N_3$. This substance, isolated by G. Tanret [1] in 1914 from the seeds of *Galega officinalis*, is best obtained as the sulphate, from which the base is prepared by decomposition with sodium hydroxide. It separates as an oil, which slowly crystallises, m.p. 60°–65°, $[\alpha]_D$ 0°, and, on exposure to air, absorbs moisture and carbon dioxide. It is monoacidic and forms well-crystallised salts ; sulphate, $B_2.H_2SO_4$, needles, m.p. 227° ; hydrochloride, B.HCl, m.p. 60°, hygroscopic ; nitrate, $B.HNO_3$, long needles, m.p. 108° ; picrate, yellow needles, m.p. 180° ; platinichloride, m.p. 123°. On distillation the free base yields 3-methylpyrrolidine, and when heated in sealed tubes with barium hydroxide gives 3-methylpyrrolidine with carbamide. It gives a dibenzoyl derivative, needles, m.p. 95°–96°, and condenses with acetylacetone to form galeginedimethylpyrimidine, m.p. 74°, and with ethyl oxalate to give oxalylgalegine, m.p. 203°–206°, together with some oxamic ester, $C_5H_9N : C(NH_2).NH.CO.CO_2Et$, prisms, m.p. 88°.

On these grounds Tanret regards galegine as constituted thus :
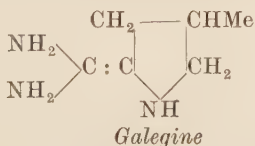
Galegine

[1] *Compt. rend.* 1914, **158**, 1182, 1426.

While this volume was in the press Barger and White[1] published the results of a re-examination of galegine in which they shewed that the base formed from it by the action of baryta is an aminoamylene (isomeric with 3-methylpyrrolidine) and that on oxidation galegine yields acetone and guanidino-acetic acid (glycocyanamine) whence they assign to it the following formula, $CMe_2 : CH.CH_2.NH.C(:NH)NH_2$, which has been accepted by Tanret, who had already considered the possibility that galegine is a guanidyl derivative of an unsaturated *iso*amylamine, but was unable to reconcile this with the production from it of what he supposed was 3-methylpyrrolidine.[2]   It is included in this volume solely because currency has been given to the view that it is a pyrrolidine derivative.

Damascenine.   The seeds of *Nigella damascena* were examined by Schneider in 1890 and found to contain a crystalline alkaloid, which was named damascenine, $C_{10}H_{15}O_3N$,[3] which was re-examined by Pommerehne,[4] who assigned to it the formula, $C_9H_{11}O_3N$, and stated that by the action of alkalis it was converted into an isomeride, damasceninic acid.   Subsequently Keller, accepting Pommerehne's results, named an alkaloid of the formula, $C_{10}H_{13}O_3N$, which he obtained from the seeds of *Nigella aristata* (*N. arvensis*), " methyldamascenine," since it could also be obtained by treating silver damasceninate with methyl iodide.[5]   Ewins repeated this work, and in addition to confirming Schneider's results has effected a synthesis of damascenine.[6]   According to Ewins, Pommerehne's " damascenine " was a mixture of Schneider's damascenine with its hydrolytic product, damasceninic acid, whilst Keller's methyldamascenine is identical with Schneider's damascenine.

For the preparation of the alkaloid, Ewins extracted the ground seeds with light petroleum and then shook out the latter directly with 5 per cent. hydrochloric acid.   From this the alkaloid was recovered by adding sodium carbonate, shaking out with ether, distilling off the solvent, and distilling the residue under reduced pressure.   The yield from the seeds was 0·32 per cent.

[1] *Bio-Chem. Journ.* 1923, **17,** 827.   *Cf.* Späth and Prokopp, *Berichte,* 1924, **47,** 174.
[2] Thèse, " Recherches chimiques et physiologiques sur la grainede Galega."   Paris, 1917 ; *Bull Soc. Chim.* 1924, **35,** 404.
[3] *Pharm. Centr.-h.* 1890, **31,** 173.
[4] *Arch. Pharm.* 1900, **238,** 531.
[5] *Ibid.* 1904, **242,** 299 ; 1908, **246,** 1.
[6] *Trans. Chem. Soc.* 1912, **101,** 544.

DAMASCENINE, $C_{10}H_{13}O_3N$, is a crystalline mass, m.p. 24°–26°, b.p. 154°/15 mm. or 270°/750 mm.   It is readily soluble in most organic solvents, giving solutions showing a blue fluorescence.   The salts crystallise well, and the forms of certain of them have been described.[1]   The hydrochloride forms triclinic crystals with $1H_2O$ from 80 per cent. alcohol, m.p. 122° or 156° (dry) ; the nitrate has m.p. 94°–95° ; the picrate crystallises in lemon-yellow rhombic plates, m.p. 158°–159°.   On hydrolysis with acids or alkalis, damascenine yields methyl alcohol and damasceninic acid, $C_9H_{11}O_3N$. The latter is a monobasic acid, and on treatment with hydriodic acid yields methyl iodide and 2-methylamino-3-hydroxybenzoic acid, whence Keller [2] has assigned to it the following formula, while Ewins [3] has shown that damascenine is the methyl ester of damasceninic acid.

Damasceninic acid (Keller)   Damascenine (Ewins)
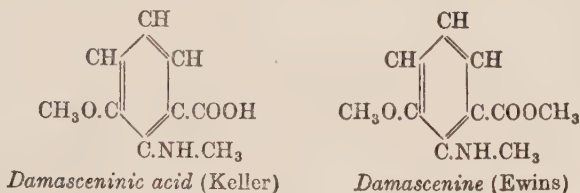
Ewins has synthesised both these substances from m-methoxy-benzoic acid, which on nitration gave 2-nitro-3-methoxybenzoic acid, and this on reduction and treatment with methyl iodide yielded 2-methylamino-3-methoxybenzoic acid identical with damasceninic acid, which on esterification with methyl alcohol furnished damascenine, identical with the natural alkaloid.   Kaufmann and Rothlen have shown that the additive product of 8-hydroxyquinoline and methyl sulphate on oxidation with permanganate yields formyl-damasceninic acid, $MeO.C_6H_3(NMe.CHO).COOH$, which can be transformed into damasceninic acid (2-methylamino-3-methoxy-benzoic acid) by warming with dilute hydrochloric acid, and the acid on esterification by methyl alcohol yields damascenine.[4]

Ephedrine and ψ-**Ephedrine**, $C_{10}H_{15}ON$.   These alkaloids were isolated by Nagai [5] and Merck [6] respectively from *Ephedra vulgaris*.

[1] Schwantke, *Zeit. Kryst. Min.* 1909, **46,** 73.
[2] *Arch Pharm.* 1904, **242,** 299 ; 1908, **246.** 1.
[3] *Trans. Chem.* Soc. 1912, **101,** 544.
[4] *Berichte,* 1916, **49,** 578.
[5] *Pharm. Zeit.* 1887, **32,** 700.
[6] *Merck's Berichte,* 1893, 13.   Cf. Miller, *Arch. Pharm.* 1902, **240,** 481.

They are under various conditions mutually convertible, *e.g.*, on boiling with hydrochloric acid an equilibrium mixture of both is formed and they are, therefore, regarded as stereoisomerides.[1]

EPHEDRINE is a colourless crystalline substance, m.p. $40°$, b.p. $225°$, $[\alpha]_D - 6\cdot3°$, soluble in alcohol ether or water. The hydrochloride forms colourless needles, m.p. $216°$, $[\alpha]_D - 36\cdot6°$ in water, the hydrobromide, m.p. $205°$, the platinichloride, $B_2 . H_2PtCl_6$, crystallises in colourless needles, m.p. $186°$, and the aurichloride, $B . HAuCl_4$, yellow needles, m.p. $128°-131°$. Ephedrine yields a dibenzoyl derivative and with methyl iodide furnishes methylephedrinemethylammonium hydroxide which on distillation breaks down into trimethylamine and α-phenylpropylene-α-β-oxide.[2]

ψ-EPHEDRINE (iso*Ephedrine*) occurs with ephedrine in *E. vulgaris*, and can be formed from it by boiling with hydrochloric acid, by acetylation and in other ways,[3] and was first investigated in detail by Ladenburg and Oelschlagel.[4]   It crystallises from ether in rhombic tablets, m.p. $114°-115°$ ($117\cdot5°$, Emde), $[\alpha]_D + 49\cdot45°$. The hydrochloride forms colourless needles, m.p. $176°$, and the aurichloride golden-yellow needles. On the grounds that the alkaloid yielded a nitrosoamine, a dibenzoyl derivative, and furnished benzoic acid on oxidation, Ladenburg and Oelschlagel assigned to it the following constitution : (I) $HO.CHPh.CHMe.NHMe$, which, since the two are stereoisomerides must also represent ephedrine. Emde [5] suggested the alternative formula (II), $CH_3.CHOH.CHPh. NHCH_3$, but Rabe's observation that the ammonium base of ephedrine yields α-phenylpropylene-α-β-oxide,[6] $\overline{CHPh.O.CHMe}$ afforded strong evidence for formula (I).

Since then work on the two alkaloids [7] has afforded further confirmation of formula (I), and finally it was proved correct by the

[1] Schmidt, *Merck's Berichte*, 1908, **246**, 210 ; 1912, **250**, 154 ; 1913, **251**, 320 ; *Apoth. Zeit.* 1913, **28**, 667.   *Cf.* Emde, *Arch. Pharm.* 1907, **245**, 662 ; and Calliess, *Apoth. Zeit.* 1910, **25**, 677 (by acetylation).

[2] Rabe, *Berichte*, 1911, **44**, 824.   *Cf.* Schmidt, *Arch. Pharm.* 1909, **243**, 73 ; 1911, **249**, 305 ; 1915, **253**, 52.

[3] Schmidt, *Arch. Pharm.* 1908, **246**, 210 ; 1912, **250**, 154 ; 1913, **251**, 320 ; *Apoth. Zeit.* 1913, **28**, 667.   *Cf.* Emde, *Arch. Pharm.* 1907, **245**, 662 ; and Calliess, *Apoth. Zeit.* 1910, **25**, 677 (by acetylation).

[4] *Berichte*, 1889, **22**, 1823.

[5] *Arch. Pharm.* 1907, **245**, 662.

[6] Rabe, *Berichte*, 1911, **44**, 824.   *Cf.* Schmidt, *Arch. Pharm.* 1909, **243**, 73 ; 1911, **249**, 305 ; 1915, **253**, 52.

[7] *See*, for example, Schmidt, *Arch. Pharm.* 1914, **252**, 89 ; 1915, **253**, 52 ; Ogata, *J. Pharm. Soc. Japan*, 1919, **451**, 751.

synthesis of both alkaloids. Though attempts to synthesise ephedrine had been made by Schmidt [1] and by Fourneau, [2] it was not until quite recently that these attempts achieved success, when Eberhardt, [3] working on the lines suggested by Schmidt's earlier work, [1] obtained inactive ephedrine and ψ-ephedrine by reducing α-methylaminopropiophenone with hydrogen in presence of palladinised charcoal, $CO.Ph.CHMe.NHMe \rightarrow HO.CHPh.CHMe.NHMe$. Fourneau [4] later on converted propenylbenzene, obtained by dehydrating phenylethylcarbinol into the corresponding bromohydrin ; this on heating with methylamine solution in sealed tubes yielded inactive ephedrine, which on acetylation was converted into ψ-ephedrine. Meanwhile Späth and Göhring [5] had achieved another synthesis, and in addition resolved the inactive products into the four optically active forms. This synthesis was effected by stages represented by the following equations :

I. $CH_3.CH_2.CHO + Br_2 = CHMeBrCHO + HBr$

II. $CHMeBr.CHO + HBr + MeOH = CHMeBr.CHBr.OMe + H_2O$

III. $CHMeBr.CHBr.OMe + MgPhBr = MeO.CHPh.CHMeBr + MgBr_2$

IV. $MeO.CHPh.CHMeBr. + NH_2Me = MeO.CHPh.CHMe.NH_2MeBr$

V. $MeO.CHPh.CHMe.NHMe + HBr = HO.CHPh.CHMe.NHMe + CH_3Br$
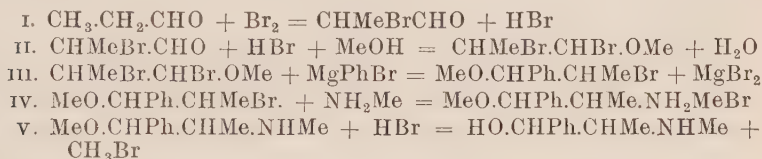
and leaves no doubt as to the constitution of the final product which consisted of inactive ψ-ephedrine, m.p. 117°–118°. This was resolved by crystallisation of the d-tartrate into l- and d-components, the latter being identical with natural ψ-ephedrine. From these components synthetic d- and l-ephedrines were obtained by heating with hydrochloric acid. It is believed that in ψ-ephedrine the HO — and — NHMe group are close together, and distant from each other in ephedrine. dl-Ephedrine has m.p. 73°–74° ; B.HCl, m.p. 188·5°–189·5° ; $[\alpha]_D^{20}$ for active forms of hydrochloride $\pm 34·5°$; dl-ψ-ephedrine has m.p. 118·2°, B.HCl, m.p. 164° ; aurichloride, $B_2.HCl–HAuCl_4$, m.p. 186°–187° ; $[\alpha]_D$ for active forms of hydrochloride $\pm 52·5°$.

Physiological Action. Ephedrine is toxic and mydriatic, and the hydrochloride has been used alone and in conjunction with homatropine to produce mydriasis. ψ-Ephedrine is also poisonous, but

[1] *Arch. Pharm.* 1905, **243**, 73 ; 1909, **247**, 141 ; *Apoth. Zeit.* 1911, No. 37.

[2] *J. Pharm. Chim.* 1904 [vi], **20**, 481 ; 1907 [vi], **25**, 593.

[3] *Arch. Pharm.* 1920, **258**, 97.

[4] (With Peyal) *Anal. Fis. Quim.* 1922, **20**, 394.

[5] *Monats.* 1920, **41**, 319.

is said to produce mydriasis when taken internally, but not when applied directly to the eye.[1]

EPHEDRINE (SPEHR), $C_{13}H_{19}ON$, isolated from *Ephedra monostachya*, crystallises in monoclinic prisms, m.p. 112°, and is said to be practically inert physiologically.[2]

Hordenine, $C_{10}H_{15}ON$, was isolated from barley malt germs (*Hordeum sativum*) by Léger,[3] who subsequently examined it in detail and assigned to it the constitutional formula given below. It also occurs in Anhalonium species (p. 194).

Hordenine forms colourless, bulky, orthorhombic prisms, melts at 117·8°, boils at 173°–174°/11 mm., sublimes at 140°–150°, is optically inactive, and is readily soluble in water, alcohol, chloroform or ether, but sparingly so in benzene. It is alkaline in reaction, liberates ammonia from its salts, behaves as a monoacidic, tertiary base, and yields well-crystallised salts ; picrate, m.p. 139°–140°, picrolonate, m.p. 219°–220° ; and a methiodide (m.p. 229°–230°). The oxygen atom is present as a phenolic hydroxyl group. On " exhaustive methylation " hordenine yields trimethylamine and *p*-vinylanisole. Acetylhordenine on oxidation furnishes *p*-acetoxybenzoic acid. On the basis of these results Léger suggested that hordenine is *p*-hydroxy-β-phenylethyldimethylamine,[4] and this was confirmed by the synthesis of hordenine effected by Barger[5] and later by Rosenmund and others.[6] Barger used as a starting-point phenylethyl alcohol, which was converted into hordenine by the following series of changes :

$$C_6H_5.CH_2.CH_2OH \longrightarrow C_6H_4.CH_2.CH_2Cl \longrightarrow C_6H_5.CH_2.CH_2.N(CH_3)_2$$

by nitration

CH CH
CH CH
$C.NO_2$
$C.CH_2.CH_2.N(CH_3)_2$

by reduction and diazotisation

CH CH
CH CH
$C.OH$
$C.CH_2.CH_2.N(CH_3)_2$
Hordenine
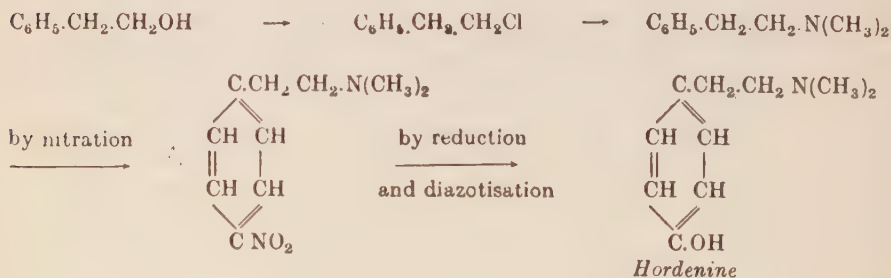
[1] *Berichte*, 1889, **22**, 1823.
[2] *Chem. Soc. Abstr.* 1892, 893.
[3] *Compt. rend.* 1906, **142**, 108 ; **143**, 234, 916 ; 1907, **144**, 208, 488, *Cf.* Torquati, *Chem. Soc. Abstr.* 1911 [ii], 253 ; Gäbel, *Arch. Pharm.* 1906. **244**, 435 ; and Hashitani, *Chem. Soc. Abstr.* 1920 [i], 360.
[4] *Cf.* Gaebel, *Arch. Pharm.* 1906, **244**, 435.
[5] *Trans. Chem. Soc.* 1909, **95**, 2193.
[6] *Berichte*, 1910, **43**, 306 ; Voswinckel, *ibid.* 1912, **45**, 1004 ; Ehrlich and

Hordenine is, therefore, closely related to p-hydroxy-β-phenylethyl-amine (p. 385) found in ergot.

According to Camus,[1] hordenine is only slightly toxic, but in large doses causes death by arrest of respiration. The alkaloid increases the blood pressure, has some diuretic action, and is hæmolytic.

N-**Methyltyrosine**, $C_{10}H_{13}O_3N$ (β-p-hydroxyphenyl-α-methylamino-propionic acid). This substance, under the names, angeline, geoffroy-ine, andirine, rhatanine and surinamine, has been isolated from *Ferreira spectabilis*, *Andira retusa*, *A. inermis*, *Geoffrœa surnamensis* and *Krameria triandra*.[2]

Sinapine, $C_{16}H_{25}O_6N$, was isolated in the form of its thiocyanate from black mustard seeds (*Brassica nigra*) by Henry and Garot [3] by precipitating a concentrated alcoholic extract of the oil-free seeds with potassium thiocyanate in alcohol, a method still employed for the isolation of the alkaloid. Will and Laubenheimer [4] first called attention to the fact that sinapine occurs in white mustard seed in the form of the alkaloidal glucoside, SINALBINE, $C_{30}H_{42}O_{15}N_2S_2$. The latter, on hydrolysis by the enzyme myrosin, also present in the seed, furnishes dextrose, p-hydroxybenzylthiocarbimide, and sina-pine sulphate.[5] Sinapine, owing to the ease with which it decomposes, is unknown in the free state. The thiocyanate is recrystal-lised from water until pure, and can be converted into the acid sulphate by treatment with sulphuric acid.

Sinapine acid sulphate, $C_{16}H_{24}O_5N.HSO_4.3H_2O$, crystallises from alcohol in leaflets, m.p. $127°$ ($188°$ *dry*). The thiocyanate, $C_{16}H_{24}O_5N.SCN.H_2O$, forms pale yellow needles, m.p. $178°$.

When the thiocyanate is warmed with alkalis there is formed choline and sinapic acid, $C_{11}H_{12}O_5$; [6] the acid was investigated by Remsen and Coale,[7] and by Gadamer.[5] It crystallises in prisms,

Pistschimuka, *ibid.* 1912, **45**, 2428 ; Späth and Sobel, *Monats.* 1920, **41**, 77 ; Kindler and Finndorf, *Annalen*, 1923, **431**, 187 ; homologues of hordenin, von Braun (and Deutsch), *Berichte*, 1912, **45**, 2504 ; 1914, **47**, 492.

[1] *Compt. rend.* 1906, **142**, 110, 237, 350 ; and *Arch. in. de Pharma-codyn et Therap.* 1906, **16**, 43.

[2] Hiller-Bombien, *Arch. Pharm.* 1892, **230**, 513 ; Blau, *Zeit. physiol. Chem.* 1908, **58**, 153. For work on constitution *see* Goldschmiedt, *Monats.* 1912, **33**, 1379 ; 1913, 34, 659 ; Friedmann and Guthmann, *Biochem. Zeits.* 1910, **27**, 491 ; Johnson and Nicolet, *Amer. Chem. Journ.* 1912, **47**, 459.

[3] *Journ. Pharm.* 1825, **20**, 63.

[4] *Annalen*, 1879, **199**, 162.

[5] *Gadamer, Arch. Pharm.* 1897, **235**, 44 ; 1897, **235**, 570 ; *Berichte*, 1897, **30**, 2322, 2327, 2328, 2330.

[6] Von Babo and Hirschbrunn, *Annalen*, 1852, **84**, 10.

[7] *Amer. Chem. Journ.* 1884, **6**, 52.

m.p. 191°–192°, contains two methoxyl groups, furnishes a mono-acetyl derivative and contains a carboxyl group. When treated with methyl iodide in presence of alkalis, it yields methyl methyl-sinapate, $(C_8H_4OMe)_3.CO_2Me$, which by partial hydrolysis with alcoholic potash forms methylsinapic acid, and from the latter there is formed by oxidation trimethylgallic acid. Acetylsinapic acid on oxidation by permanganate yields syringic acid (3 : 5-dimethoxy-4-hydroxybenzoic acid).

Gadamer [1] has proposed the following formulæ for sinapic acid and sinapine, the latter being the choline ester of sinapic acid :

$$CH$$
$$CH_3O.C \quad C.CH=CH.COOH$$
$$HO.C \quad CH$$
$$C.OCH_3$$

Sinapic acid (Gadamer)

$$CH$$
$$CH_3O.C \quad C.CH=CH.CO.O.CH_2.CH_2.N(OH)(CH_3)_3$$
$$HO.C \quad CH$$
$$C.OCH_3$$
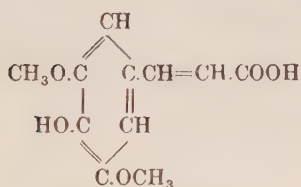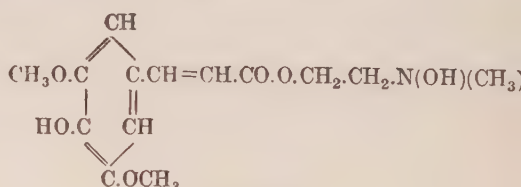
Sinapine (Gadamer)

and this has been confirmed by Späth's synthesis [2] of the quaternary iodide corresponding to sinapine by the following method. The trimethyl ether of gallic acid when heated with hydrobromic acid suffers demethylation of the methoxy group in position 4, giving syringic acid (4-hydroxy-3 : 5-dimethoxybenzoic acid), which was then converted into carbethoxysyringic acid, and this through the acid chloride into the aldehyde, $CHO.C_6H_2(OMe)_2.O.CO_2Et$. This on heating with malonic and acetic acids yielded 4-carbethoxy-3 : 5-dimethoxybenzylidenemalonic acid, $C(CO_2H)_2 : CH.C_6H_2(OMe)_2.O.CO_2Et$, which on distillation *in vacuo* lost carbon dioxide and furnished carbethoxysinapic acid, $CO_2H.CH : CH.C_6H_2(OMe)_2.O.CO_2Et$, from which the acid was obtained by hydrolysis with sodium hydroxide *in vacuo*. The last stage, esterification of the acid with choline, could not be carried out, but dimethylhydroxyethylamine with acetylsinapoylchloride gave the corresponding acetyl ester, $NMe_2.CH_2.CH_2.O.CO.CH : CH.C_6H_2(OMe)_2.OAc$, from which the acetyl group was readily eliminated yielding a product, which on treatment with methyl iodide was converted into sinapine methiodide, $NMe_3I.CH_2.CH_2.O.CO.CH : CH.C_6H_2(OMe)_2.OH$, identical with that obtainable from the natural alkaloid.

[1] *Gadamer, Arch. Pharm.* 1897, **235**, 44 ; 1897, **235**, 570 ; *Berichte,* 1897, **30**, 2322, 2327, 2328, 2330.
[2] *Monats.* 1920, **41**, 271.

For other bases of this group occurring in plants, *see under* solanaceous alkaloids (p. 62), anhalonium alkaloids (p. 194), and ergot (p. 382).

Cheiranthus and Erysimum spp.

Cheiroline. In 1898, Reeb obtained from the leaves and seeds of the wallflower two substances, which he named cheiranthin and cheirinine. The former was described as a glucoside, having a physiological action akin to that of digitalis, whilst cheirinine was given the formula, $C_{18}H_{35}O_{17}N_3$, and was stated to resemble quinine in physiological action.[1] In 1908 Wagner [2] obtained from the seeds CHEIROLINE, $C_9H_{16}O_7N_2S_2$, crystallising in colourless prisms, m.p. $46°-48°$, which, like Reeb's cheirinine, resembles quinine in physiological action, and when warmed with mercuric oxide and water yields cheirole, $C_9H_{20}O_9N_2$, colourless needles, m.p. $172.5°$.

Schneider [3] showed that Wagner's cheiroline should be represented by the formula $C_5H_9O_2NS_2$, and proved that the substance was identical with methyl-γ-thiocarbimidopropylsulphone, $CH_3 . SO_2 . (CH_2)_3 . NCS$. Cheiroline appears to exist in wallflower seed as a glucoside. It has also been obtained from the seeds of *Erysimum nanum compactum aureum* [4] and *E. arkansanum*,[5] whilst Schneider and Kaufmann have obtained from *Erysimum perowskianum*,[6] erysoline, $C_6H_{11}O_2NS_2$, which occurs in the plant as a glucoside and which they have shown by synthesis to be methyl-δ-thiocarbimidobutylsulphone, $CH_3 . SO_2 . (CH_2)_4 . NCS$.

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[1] *Arch. exp. Path. Pharm.* 1898, **41**, 302 ; 1899, **43**, 130.
[2] *Chem. Zeit.* 1908, **32**, 76.
[3] *Berichte*, 1908, **41**, 4466; 1909, **42**, 3416 ; *Annalen*, 1910, **375**, 207.
[4] *Cf.* Schlagdenhauffen and Reeb, *Compt. rend.* 1900, **131**, 753.
[5] *Berichte*, 1908, **41**, 4466; 1909, **42**, 3416; *Annalen.*, 1910, **375**, 207.
[6] *Annalen,* 1912, **392**, 1.

X. ALKALOIDS OF UNKNOWN CONSTITUTION

THE ACONITE ALKALOIDS

THE genus *Aconitum* includes a large number of species of which comparatively few have been examined. Among these is the common monkshood or wolf's bane, *Aconitum Napellus*, the toxic properties of which have been known from very early times ; preparations of aconite roots are stated to have been used as arrow poisons by the Chinese,[1] and probably also by the aborigines of ancient Gaul.[2] The drug was first employed in medicine in the thirteenth century, and was introduced into regular practice in Vienna about 1762. *Aconitum Napellus* is widely distributed in the mountainous districts of Europe and the Pacific coast of North America. In Great Britain its natural occurrence is limited to a few districts in the West of England and South Wales, although it has been cultivated to some extent for use in medicine, and is common as a garden plant.

Two other species, *Aconitum Lycoctonum* (*A. vulparia*)[3] and *Aconitum septentrionale*, which are both common in the mountainous districts of Europe, are now known to contain poisonous alkaloids of the aconitine type.

In India an interesting group of aconites occurs, which was examined botanically in 1905 by Stapf.[4] It includes *A. chasmanthum*, *A. spicatum*, *A. deinorrhizum*, and *A. Balfourii*, all known to be poisonous, and *A. heterophyllum* and *A. palmatum*, which are not toxic. The " bikh " or " bish " aconite root, which has reached Europe from India at various times under the name " Nepaul aconite," has been stated to be the root of *A. spicatum*[5] or of *A. laciniatum*, but the " Nepaul aconite " of European commerce has

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[1] Smith, *Nat. Med. and Nat. Hist. of China*, 1871.
[2] *Pharmacographia*, p. 8.
[3] Carr has suggested on the authority of Stapf that the *A. Lycoctonum* of some authors is *A. vulparia* (Allen's *Organic Analysis*, 4th ed. vol. vi., p. 255.).
[4] *Annals of the Royal Botanic Garden, Calcutta*, 1905, **10**, Part 2.
[5] Stapf, *loc. cit.* ; Watt, *Agric. Ledger, India*, 1902, No. **3**.

PLATE V.
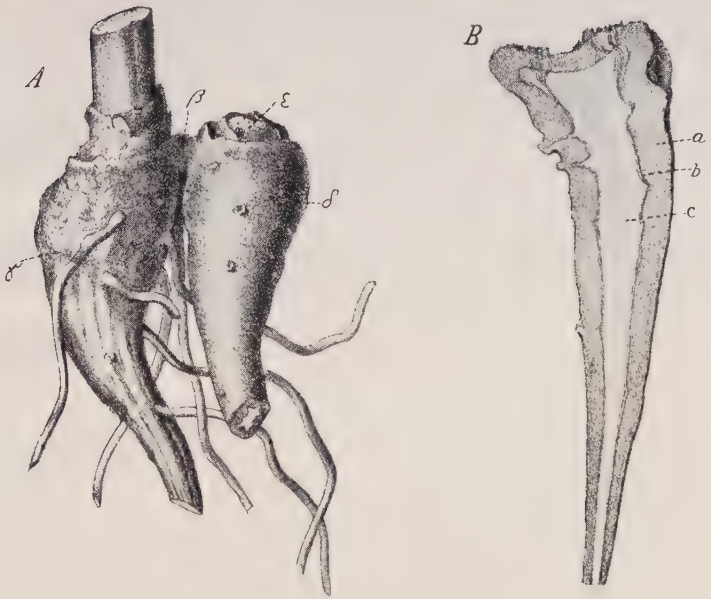
FIG. 1.—Aconite root. *A*, parent and daughter roots of the autumnal plant connected together : *γ*, parent root ; *δ*, daughter root ; *β*, short branch connecting them ; *ε*, bud at the apex of the daughter root ; natural size. *B*, longitudinal section through the daughter root. (Berg.)

FIG. 2.—Aconite herb. *a*, leaf ; *b*, flower ; *c*, *d*, petals. Three-fourths natural size. (Holmes.)

always yielded the alkaloid pseudaconitine, and so far as is known at present this alkaloid is only obtained from the roots of *A. deinorrhizum* and *A. Balfourii*.[1]

The source of the Japanese aconite, which is occasionally imported into Europe, is still uncertain. This material yields the characteristic and well-defined alkaloid japaconitine. According to Makoshi [2] two sorts of aconite roots are in use in Japan : the one known as " bushi," grown in Hokkaido (Jeso), is from *A. Fischeri* and yields jesaconitine, whilst the other is from a variety of *A. Fischeri* grown in Hondo and yields japaconitine. It is the latter which reaches Europe as Japanese aconite, and according to Holmes, it is the product of *A. uncinatum* var. *japonicum*.

Those aconite alkaloids which have been fully examined are now known to belong to three well-defined groups, viz., (1) aconitines, which are highly poisonous ; (2) decomposition products of the aconitines, which are scarcely toxic in the ordinary sense ; and (3) the atisines, which are not toxic. The principal members of these groups are as follows :

ACONITINES :

Aconitine, acetylbenzoylaconine, from *A. Napellus*.

Bikhaconitine, acetylveratroylbikhaconine, from *A. spicatum*.

Indaconitine, acetylbenzoylpseudaconine, from *A. chasmanthum*,

Japaconitine, acetylbenzoyljapaconine, from Japanese aconite roots (Hondo sort).

Pseudaconitine, acetylveratroylpseudaconine, from *A. deinorrhizum* and *A. Balfourii*.

Jesaconitine, benzoylanisoylaconine, from Japanese aconite roots (" bushi " sort).

Lappaconitine, acetylanthranoyllappaconine, from *A. septentrionale*.

Lycaconitine, succinylanthranoyllycoctonine, from *A. lycoctonum*.

DECOMPOSITION PRODUCTS OF THE ACONITINES :

(1) *Acylaconines :*

Benzaconine (benzoylaconine), from aconitine.

Veratroylbikhaconine, from bikhaconitine.

Indbenzaconine (benzoylpseudaconine), from indaconitine.

[1] For a full discussion of the alkaloids of the Indian aconites, *see* the *Bulletin of the Imperial Institute*, 1906, **4,** 32.

[2] *Arch. Pharm.* 1909, **247,** 243.

Japbenzaconine, from japaconitine.
Veratroylpseudaconine, from pseudaconitine.
Picrolappaconitine (anthranoyllappaconine), from lappaconitine.
Anthranoyllycoctonine, from lycaconitine.

(2) *Aconines :*

Aconine, from aconitine and jesaconitine.
Bikhaconine, from bikhaconitine.
Pseudaconine, from indaconitine and pseudaconitine.
Japaconine, from japaconitine.
Lappaconine, from lappaconitine.
Lycoctonine, from lycaconitine.

ATISINES :

Atisine, from *A. heterophyllum.*
Palmatisine, from *A. palmatum.*

The " aconitines " are diacyl esters of polyhydroxyamino-alcohols, the " aconines," and their structure, as known at present, is shown in the following extended formulæ :

Bikhaconitine : Acetylveratroylbikhaconine,
$$C_{21}H_{27}ON(OAc)(OVe)(OCH_3)_4$$

Indaconitine : Acetylbenzoylpseudaconine,
$$C_{21}H_{27}O_2N(OAc)(OBz)(OCH_3)_4$$

Pseudaconitine : Acetylveratroylpseudaconine,
$$C_{21}H_{27}O_2N(OAc)(OVe)(OCH_3)_4$$
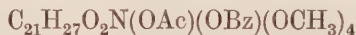
Aconitine : Acetylbenzoylaconine,
$$C_{21}H_{27}O_3N(OAc)(OBz)(OCH_3)_4$$
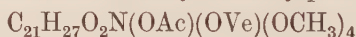
Japaconitine : Acetylbenzoyljapaconine,
$$C_{21}H_{29}O_3N(OAc)(OBz)(OCH_3)_4$$
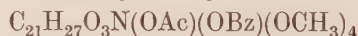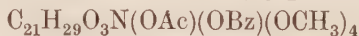
Lycaconitine : Lycoctonyllycoctonine,
$$C_{21}H_{25}O_3N(OLy)(OCH_3)_4$$

Lappaconitine : Acetylanthranoyllappaconine,
$$C_{21}H_{29}O_4N(OAc)(OAn)(OCH_3)_2$$
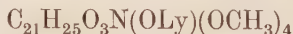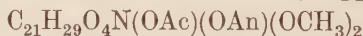
Ac = *acetyl ;* Bz = *benzoyl ;* Ve = *veratroyl ;*
Ly = *lycoctonyl* (p. 370) ; An = *anthranoyl.*

It appears, therefore, that the " aconitines " may all be regarded as derived from a parent base, $C_{21}H_xN$,[1] where $x = 31, 33,$ or 35.

[1] Dunstan and Henry, *Trans. Chem. Soc.* 1905, **87, 1655.**

Aconitum Napellus

The presence of alkaloidal constituents in *Aconitum Napellus* was first indicated with certainty by Geiger and Hesse,[1] and later an amorphous alkaloid was isolated by von Planta.[2] Pure crystallised aconitine was first probably prepared in 1860 by Groves.[3] The alkaloid was further investigated by Wright and collaborators,[4] who prepared several of its salts and examined its hydrolytic products, and later on by Dunstan and his collaborators, and by Freund and co-workers.[5]

Preparation. Aconitine may be prepared by extracting the finely ground roots with alcohol, distilling off the bulk of the solvent under reduced pressure, and shaking the faintly acid aqueous extract with ether to remove oily and resinous matters. The aqueous liquor is next made slightly alkaline by the addition of ammonia or sodium bicarbonate, and the aconitine (with small quantities of benzaconine) extracted by shaking with ether, the aconine and the greater portion of the benzaconine remaining dissolved in the aqueous layer. The ethereal solution is washed once with water, dried over anhydrous sodium sulphate, which must be neutral in reaction, and then on evaporation much of the aconitine crystallises out, and is freed from a small amount of associated resinous impurity by conversion into the hydrobromide, which is recrystallised from water until of constant melting-point, and from this the alkaloid is regenerated and crystallised from alcohol with, if necessary, addition of ether, in which it is sparingly soluble. The amorphous residue from these crystallisations contains benzaconine, of which more with some aconine can be obtained by extracting the original mother liquors with chloroform.

Properties. Wright and Luff assigned the formula, $C_{33}H_{43}O_{12}N$, to aconitine, and this was adopted subsequently with negligible modifications by Jürgens [6] and by Dunstan and his co-workers.[7] The source of the alkaloid used by Wright and by Dunstan was *A. Napellus* root cultivated in England. In 1894 Freund and Beck [8]

[1] *Annalen*, 1833, **7**, 276.

[2] *Ibid.* 1850, **74**, 257.

[3] *Pharm. Journ.* 1860 [ii], **8**, 121.

[4] *Journ. Chem. Soc.* 1875, **29**, 1265 ; 1877, **31**, 143 ; 1878, **33**, 151, 318 ; 1879, **35**, 387.

[5] For a good historical account of the early investigations, *see* Schulze, *Arch. Pharm.* 1906, **244**, 136.

[6] *Inaug. Diss.* Dorpat, 1885.

[7] *Trans. Chem. Soc.* 1891, **59**, 271 ; 1892, **61**, 385

[8] *Berichte* 1894, **27**, 433.

questioned the accuracy of this formula, and, working with commercial German aconitine, suggested the formula, $C_{34}H_{47}O_{11}N$, which was subsequently modified by Schulze to $C_{34}H_{45}O_{11}N$.[1] Schulze's formula for aconitine extracted from German aconite roots was accepted by Dunstan and Henry in 1905,[2] who then pointed out that this aconitine of German origin may not be identical with that obtained from *A. Napellus* roots grown in England.

Since then Schulze has asserted [3] that the two alkaloids must be identical, since his aconitine possessed the same crystallographic characters as were ascribed by Tutton [4] to Dunstan's aconitine, but this is not conclusive evidence, since indaconitine [5] has the same crystalline form as aconitine, but is not identical with that alkaloid. The following data are mostly those recorded by Schulze.[6]

Aconitine, $C_{34}H_{45}O_{11}N$, or $C_{34}H_{47}O_{11}N$, m.p. 197°–198°, $[\alpha]_D +$ 14·61° in chloroform, crystallises in prisms belonging to the rhombic system (a : b : c = 0·54492 : 1 : 0·38917), is soluble in chloroform or benzene, less so in ether or dry alcohol, and almost insoluble in water or light petroleum. The salts crystallise well and are lævorotatory : the hydrobromide, B . HBr, forms hexagonal tablets from water with $2\frac{1}{2}H_2O$ (it sinters at 160° and melts at 200° or at 206°–207° if dried at 115°–120°), or from alcohol and ether in minute needles with $\frac{1}{2}H_2O$, m.p. 206°–207° ; this salt has $[\alpha]_D - 30°$ 48′ in water ; the hydriodide, m.p. 226°, is sparingly soluble in water ; the hydrochloride has m.p. 149° and $[\alpha]_D - 30·9°$ in water ; the aurichloride, B . HCl . AuCl$_3$. 3H$_2$O, m.p. 136·5° or 152° (dried at 115°), crystallises in golden-yellow needles.

Aconitine contains four methoxyl groups and a methylimino group : with cold acetyl chloride it yields a triacetyl derivative, m.p. 207°–208°, crystallising from alcohol in colourless needles : aurichloride, amorphous.

When a salt of aconitine is heated at 120°–130° in aqueous solution under pressure it undergoes hydrolysis in two stages, yielding first acetic acid and a new base, *benzoylaconine* (picraconitine isaconitine, benzaconine), and eventually benzoic acid and *aconine :* these two bases also occur as such in the plant.

[1] *Apoth. Zeit.* 1904, **18**, 783 ; 1905, **20**, 368. *Cf.* Schmidt, *Arch. Pharm.* 1909, **247**, 233.
[2] *Trans. Chem. Soc.* 1905, **87**, 1653.
[3] *Arch. Pharm.* 1906, **244**, 169.
[4] *Trans. Chem. Soc.* 1891, **59**, 233.
[5] Dunstan and Andrews, *ibid.* 1905, **87**, 1622.
[6] *Arch. Pharm.* 1906, **244**, 136, 165 ; 1908, **246**, 281.

$$C_{34}H_{45}O_{11}N + H_2O = CH_3.COOH + C_{32}H_{43}O_{10}N$$

Aconitine   Acetic acid   Benzoylaconine

$$C_{32}H_{43}O_{10}N + H_2O = C_6H_5.COOH + C_{25}H_{39}O_9N$$

Benzoylaconine   Benzoic acid   Aconine
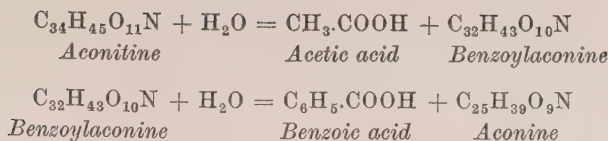
When water is replaced by methyl alcohol, acetic acid is split off and methylbenzoylaconine, m.p. 210°–211°,[1] is formed.

Aconitine may, therefore, be represented by the following extended formula :

$$(HO)_3 \diagdown$$
$$\qquad C_{20}H_{21}NMe \diagup^{O.CO.C_6H_5}_{\diagdown O.CO.CH_3}$$
$$(CH_3O)_4 \diagup$$
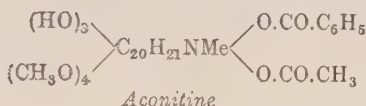
Aconitine

On oxidation with permanganate in acetone in presence of acetic acid aconitine is oxidised to acetaldehyde and oxonitine ; the formula of the latter may be $C_{24}H_{29}O_9N$, $C_{24}H_{31}O_9N$, $C_{22}H_{29}O_8N$, or $C_{27}H_{35}O_8N$, of which the first is on the whole most probable.[2] This substance crystallises in stout, well-formed prisms, on adding acetone to its solution in boiling acetic acid, has m.p. 276°–277° (bath first heated to 260°), $[\alpha]_D - 62°$ in chloroform, is sparingly soluble in ordinary solvents, tasteless, neutral in reaction, does not combine with acids or alkalis, and is not precipitated by ordinary alkaloidal reagents. It is unaffected by bromine, methyl iodide, hydroxylamine or acetic anhydride, contains the acetyl- and benzoyl-groups of aconitine intact, and retains three out of the four methoxyl groups originally present in that alkaloid. Assuming that the : NCH_3 group of aconitine is also present, the first formula given above may be extended thus, $C_{11}H_9O_2N(CH_3)(O.Bz)(O.Ac)(OMe)_3$. On reduction with phosphorus and hydriodic acid oxonitine yields a crystalline substance, m.p 121°–122°, b.p. 200°/15 mm., which is probably of simple constitution.[2]

With fuming nitric acid both aconitine and oxonitine (Barger and Field) are converted into a nitrosodicarboxylic acid, $C_{22}H_{26}O_{11}N_2$, which separates from alcohol as an orange-yellow crystalline powder, m.p. 205°. This also retains the acetyl- and benzoyl-groups intact, and contains two out of the three methoxyl groups present in oxonitine. It is oxidisable by permanganate, but only dimethylamine, acetic and benzoic acids have yet been recognised among the

[1] Dunstan, Tickle and Jackson, Proc. Chem. Soc. 1896, p. 159.
[2] Barger and Field, Trans. Chem. Soc. 1915, 107, 231. Cf. Carr, ibid. 1912, 101, 2241 ; Brady, ibid. 1913, 103, 1821.

oxidation products.   From its behaviour its formula may, according
to Brady, be extended as follows : $C_8H_7N.(CH_3)(O.Bz)(O.Ac)(OMe)_2$
$(COOH)_2(NO)$.

BENZOYLACONINE (*Benzaconine*), $C_{32}H_{43}O_{10}N$, m.p. 130°, is
amorphous, but yields crystalline salts.   Like aconitine it is dextro-
rotatory, $[\alpha]_D + 5°\ 37'$, but furnishes lævorotatory salts ; the
hydrobromide, m.p. 273°, crystallises from dilute hydrobromic acid
in thick colourless prisms ; the hydriodide has m.p. 204°–205° ; the
hydrochloride occurs in two forms, m.p. 217° and m.p. 270°.   The
aurichloride is amorphous, m.p. 125°–135°.

On acetylation benzoylaconine yields a tetracetyl derivative,
m.p. 207°–208°, which Schulze states is identical with triacetyl-
aconitine.

ACONINE, $C_{25}H_{39}O_9N$, m.p. 132°, the final basic product of
hydrolysis, has not been obtained crystalline, being hygroscopic, as
are also its salts.   The alkaloid is dextrorotatory, $[\alpha]_D + 23°$ in
water, but yields lævorotatory salts.   The hydrobromide, $B.HBr.$
$1\frac{1}{2}H_2O$, m.p. 225° (*dry*), and the hydrochloride, $B.HCl.2H_2O$,
m.p. 175°–176° $[\alpha]_D - 7·7°$ in water, are both crystalline, but the
aurichloride is amorphous.   Tetracetylaconine, m.p. 231°–232°, is
crystalline.   Aconine contains four methoxyl groups and a methyl
linked to nitrogen.

According to Schulze,[1] aconine, on oxidation with chromic acid,
yields acetaldehyde, methylamine and two nitrogenous substances,
one basic, $C_{24}H_{35}O_8N$, and the other, $C_{24}H_{33}O_9N$, having both basic
and acidic properties, which it is suggested are related to each other
as amino-alcohol and amino-acid.   The former yields a crystalline
hydrochloride, $C_{24}H_{35}O_8N.HCl.3H_2O$, m.p. 213° or 220° (*dry,
decomp.*), $[\alpha]_D^{20} + 54·37°$ in water, in slender colourless needles and a
hydriodide, $B.HI.3H_2O$, m.p. 222° (*decomp.*).   The aurichloride and
other salts are amorphous.   It contains three methoxyl groups,
yields a tetracetyl derivative, m.p. 233° (*decomp.*), and a methiodide,
needles, m.p. 222° (*decomp.*).   On further oxidation a minute
quantity of the amino-acid was obtained.   The latter yields a
crystalline hydrochloride, $C_{24}H_{33}O_9N.HCl.\frac{1}{2}H_2O$, m.p. above 250°
(*decomp.*), a crystalline barium salt, $B_2.Ba.10H_2O$, and a crystalline
methyl ester hydrochloride, m.p. 215°–220° (*decomp.*), the formula
of which may be extended thus : $C_{19}H_{20}O_4(OMe)_3(NMe).CO_2Me.$
$HCl.3H_2O$, whilst that of the basic substance may be written as
follows : $C_{20}H_{19}O.(OAc)_4.(OMe)_3.NMe$.

[1] *Arch. Pharm.* 1906, **244**, 136 ; 1908, **246**, 281.

When heated at its melting-point aconitine loses one molecule of acetic acid and gives rise to a new alkaloid, *pyraconitine*, $C_{32}H_{43}O_9N$, m.p. 167·5° (171° Schulze), colourless, slender needles, $[\alpha]_D^{20} - 112·2°$ in alcohol (Schulze and Liebner), but yields crystalline lævorotatory salts. Pyraconitine is very readily hydrolysed by alkalis, yielding benzoic acid and *pyraconine*, which is lævorotatory and amorphous, but yields a crystalline, lævorotatory hydrochloride, m.p. 154°, $[\alpha]_D - 102°$ in water [1] (m.p. 134°–135°, $[\alpha]_D - 124·6°$, S. and L.).

Aconitine is most readily detected by the tingling sensation produced when a drop of a very dilute solution is applied to the tip of the tongue. This test must be used with caution owing to the highly toxic character of the alkaloid. It furnishes with permanganate in presence of a little acetic acid an unstable precipitate of rosettes of purple needles.[2] These reactions are also given by the other aconitines, and for the identification of any individual aconitine isolation of the alkaloid, preparation of one or more of its crystalline derivatives and the determination of their melting-points and other typical constants are desirable.

Estimation. The British and United States Pharmacopœias both prescribe methods for the estimation of the ether-soluble alkaloids of aconite root, but as these include benzaconine, the processes are only of value as indicating that the drug is not adulterated if it comes up to the standard specified. They afford no real indication of the amount of aconitine present, and so far no satisfactory chemical method of estimating aconitine has been devised. The United States Pharmacopœia supplements this crude assay process by requiring that the galenical preparations of aconite should pass a biological test, *i.e.*, the fluid extract of aconite should kill guinea-pigs when administered in a dose of 0·00004 c.c., the tincture in a dose of 0·0004 c.c., and the extract in a dose of 0·00001 grm. ; in each case the lethal dose is per gramme of body-weight of the animal used.

Physiological Action. Aconitine is highly toxic : it at first stimulates the medullary centres slowing the heart ; acceleration follows, auricles and ventricles taking up an independent rhythm. The alkaloid at first stimulates and finally depresses the respiratory centre, and in mammals produces death by central respiratory failure. The motor and reflex nervous systems are at first stimu-

[1] Dunstan and Carr, *Trans. Chem. Soc.* 1894, **65**, 176 ; Schulze and Liebner, *Arch. Pharm.* 1913, **251**, 453 ; 1916, **254**, 567.
[2] Dunstan and Carr, *Pharm. Journ.* 1896, **56**, 122.

lated, but eventually depressed.   The alkaloid induces lowering of
internal temperature.   The lethal dose per kilogramme of body-
weight is : for rabbits 0·000139 grm., for guinea-pigs 0·00012
grm., and for frogs (*Rana temporaria*) 0·000586 (March) to 0·0014
(July) grm.[1]

Benzoylaconine.   The toxicity of this alkaloid is slight as com-
pared with that of aconitine.   The main physiological action is
somewhat antagonistic to that of the parent alkaloid.   Benzoyl-
aconine slows the action of the heart, and especially of the ventricles;
it depresses the respiratory centres from the first, but its effect on
respiration and internal temperature is on the whole similar to,
but far less marked than, that of aconitine.   The lethal dose for
frogs is 0·284 grm. per kilogramme of body-weight.[1]

Pyraconitine induces slowing of the action of the heart, depresses
the activity of the respiratory centres, and is from five to six times
as toxic as benzoylaconine towards frogs.[2]

Methylbenzoylaconine causes slowing of the heart, and in large
doses failure in sequence.   The cardiac vagus is depressed in action,
and its inhibitory function is ultimately suspended.   Motor nerves
are greatly affected by doses which are distinctly below the lethal
for cold-blooded animals, the action being curare-like in character.
The toxicity of aconitine is from 80 to 100 times greater than that
of methylbenzoylaconine, whilst the latter is from three to four
times more toxic (towards rabbits) than benzoylaconine.

Aconine behaves as a cardiac tonic and is antagonistic to aconitine
in a much greater degree than is benzoylaconine.   It exerts a curare-
like effect on the motor nerve endings of muscles.   The lethal dose
for frogs is 1·055 to 1·75 grm. per kilogramme of body-weight.[1]

These results show that the powerful toxicity of aconitine is
correlated with the presence of the acetyl group ; thus benzoyl-
aconine in its action on the heart is antagonistic to aconitine, though
in its influence on the respiration and temperature it still retains
traces of the depressant action of the parent alkaloid.   Pyraconitine,
produced by the action of heat on aconitine, resulting in the loss of
a molecule of acetic acid, differs from benzoylaconine by the elements
of water.   It resembles benzoylaconine generally in its physiological
action, though it is rather more toxic.   Methylbenzoylaconine is
aconitine in which the acetyl group is replaced by methyl.   Though
methylbenzoylaconine is more toxic than benzoylaconine, it is a very

[1] Cash and Dunstan, *Phil. Trans.* 1898, **190**, 239.
[2] Cash and Dunstan, *ibid.* 1902, **195**, 97.

feeble poison when compared with aconitine. The introduction of the methyl group induces a curare-like action. The removal of the benzoyl group from benzoylaconine gives rise to aconine and still further reduces the toxicity, and aconine, in a much greater degree than benzoylaconine, is antagonistic to aconitine, so much so that the administration of aconine is successful in averting in small animals the effect of a lethal dose of aconitine. Perhaps the most characteristic feature of the physiological action of aconine is the curare-like effect on the motor nerve endings of the muscles. Aconine is not poisonous in the usual sense, very large doses being required to produce death, even in frogs.

Japanese Aconites

The Japanese aconite roots of European commerce are usually regarded as identical with those known as " kusauzu " in Japan, and are generally stated to be derived from *Aconitum Fischeri*, though their exact botanical origin is by no means settled. Makoshi states [1] that at least two kinds of aconite roots are known as " kusauzu " in Japan, the one occurring in Hondo, and the other found in China and the island of Hokkaido (Jeso) in Japan. The former is used in medicine, and the latter was formerly employed as an arrow poison. The same author finds that the Hondo " kusauzu " roots contain japaconitine, and the Hokkaido " kusauzu " or " bushi " roots contain a different alkaloid, jesaconitine. Makoshi quotes Miyabe as stating that the Hokkaido roots are derived from typical *Aconitum Fischeri*, and the Hondo roots from a variety of *A. Fischeri*. In this connection it may be mentioned that *A. chasmanthum*, Stapf, of India, was formerly regarded as a variety of *Aconitum Napellus*, and in the same way it seems likely that the Hondo plant may prove on further examination to be a species distinct from *A. Fischeri*, and Makoshi's observation that the alkaloids from the Hondo and Hokkaido roots are different is useful evidence in favour of this supposition. According to Holmes, the Japanese aconite of European commerce is probably derived from *Aconitum uncinatum* var. *japonicum*.

Japaconitine, $C_{34}H_{49}O_{11}N$. Japaconitine was first obtained crystalline by Paul and Kingzett,[2] and was subsequently investigated by Wright, Luff, and Menke,[3] who prepared crystalline salts

[1] *Arch. Pharm.* 1909, **247,** 243.
[2] *Pharm. Journ. and Trans.* 1877 [iii], **8,** 173.
[3] *Trans. Chem. Soc.* 1879, **35,** 387.

of the alkaloid, observed its hydrolysis into benzoic acid and amorphous japaconine, and assigned to it the formula, $C_{66}H_{88}O_{21}N_2$, regarding it as a sesqui-apo-derivative of a hypothetical base of the formula, $C_{33}H_{47}O_{12}N$. Later observers, Mandelin,[1] Lübbe,[2] and Freund and Beck,[3] concluded that the alkaloid of Japanese aconite was identical with aconitine. Dunstan and Read,[4] on the contrary, found that japaconitine is closely allied to, but not identical with, aconitine, and this has been confirmed by Makoshi.[5] Pope [4] and Schwantke [6] have shown that japaconitine is crystallographically distinct from aconitine.

Japaconitine may be prepared by the method described under aconitine (p. 355) ; it forms colourless rosettes of needles, and melts at 204·5° (corr.), $[\alpha]_D + 20·26°$ in chloroform or $+ 23·6°$ in alcohol, is soluble in chloroform, hot ether, or hot alcohol, but insoluble in light petroleum or water. The salts crystallise from alcohol on addition of ether ; their solutions are lævorotatory ; the hydrochloride, $B.HCl.3H_2O$, separates from water in rosettes of hexagonal plates, m.p. 149°–150°, $[\alpha]_D — 23·8°$ in water ; the hydrobromide, rosettes of hexagonal plates, $B.HBr.4H_2O$, m.p. 172°–173° ; the nitrate, $B.HNO_3$, minute rosettes, m.p. 173°–177° (from water), or from alcohol and ether, 194°, and the thiocyanate, $B.HCNS$, lustrous needles, m.p. 190°–192°. The aurichloride, $B.HAuCl_4$, occurs in two forms : the α-form, which is the more stable, and separates from alcohol on addition of ether or water, in golden-yellow rosettes, m.p. 231° ; and the β-form, obtained by spontaneous evaporation of solutions in chloroform, which crystallises in yellow prisms, m.p. 154°–160°. Japaconitine and its salts, like aconitine, cause, even in very dilute solution, an intense tingling when applied to the tip of the tongue. Japaconitine contains four methoxyl groups ; it combines with methyl iodide, forming a methiodide, m.p. 224°–225°, which on treatment with dilute potash produces methyljapaconitine, $C_{34}H_{48}O_{11}NCH_3$; this crystallises from ether in needles, m.p. 206°. Acetyl chloride in the cold converts the alkaloid into triacetyljapaconitine, crystallising in rosettes, m.p. 166° (Dunstan and Read), 188° (Makoshi). Japaconitine, on hydrolysis, furnishes at first one molecular proportion of acetic acid and *jap-*

[1] *Arch. Pharm.* 1885, **23**, 162.
[2] *Chem. Central.* 1890 [ii], 148.
[3] *Berichte*, 1894, **27**, 723.
[4] *Trans. Chem. Soc.* 1900, **77**, 49.
[5] *Loc. cit.*
[6] *Arch. Pharm.* 1909, **247**, 242.

benzaconine (benzoyljapaconine), $C_{32}H_{47}O_{10}N$; the latter is to some extent further hydrolysed, producing benzoic acid and *japaconine*, $C_{25}H_{43}O_9N$, in equimolecular quantities.

JAPBENZACONINE (benzoyljapaconine), $C_{32}H_{47}O_{10}N$, crystallises from ether by addition of light petroleum in minute rosettes, m.p. 183°, $[\alpha]_D + 40 \cdot 16°$ in alcohol. The salts crystallise well and are lævorotatory; the hydrochloride, $B \cdot HCl \cdot H_2O$, forms small rosettes, m.p. 253°; the hydrobromide, $B \cdot HBr$, m.p. 205°–217°; the aurichloride, $B \cdot HAuCl_4$, crystallises from dry alcohol and then melts at 219°; when crystallised from alcohol by addition of light petroleum, it is converted into aurichlorjapbenzaconine, $C_{32}H_{46}O_{10}N \cdot AuCl_2$, colourless octahedra, m.p. 178°. Tetracetyljapbenzaconine, m.p. 231°–232°, forms compact transparent crystals (Makoshi).

JAPACONINE, $C_{25}H_{43}O_9N$, best obtained by hydrolysing japbenzaconine with alcoholic soda, is a colourless, hygroscopic powder, m.p. 99°–100°, $[\alpha]_D + 10 \cdot 8°$ in water, insoluble in ether or light petroleum, but soluble in water, alcohol, or chloroform; $[\alpha]_D + 10 \cdot 8°$ in water. The salts crystallise with difficulty, the hydrobromide from alcohol and ether in triangular plates, m.p. 221°.

Japaconitine may be represented by the following extended formula:

$$\begin{matrix} (HO)_3 \\ \\ (CH_3O)_4 \end{matrix} \Big\rangle C_{21}H_{26}N \Big\langle \begin{matrix} O.CO.CH_3 \\ \\ O.CO.C_6H_5 \end{matrix}$$
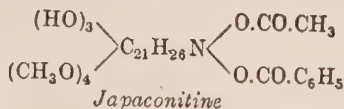
Japaconitine

The close relationship of this alkaloid to aconitine is shown by the fact that it also yields oxonitine by oxidation with permanganate (*see* p. 357).

PYROJAPACONITINE, $C_{32}H_{45}O_9N$, is formed when japaconitine is heated at its melting-point, a molecule of acetic acid being split off. It crystallises in needles, m.p. 167°–168°, $[\alpha]_D - 65 \cdot 8°$ in alcohol. The hydrobromide, $B \cdot HBr \cdot 2H_2O$, crystallises from water in colourless needles, m.p. 241°, $[\alpha]_D - 102 \cdot 5°$ in water; the aurichloride, $B \cdot HAuCl_4$, is crystalline, m.p. 160°–161°, from chloroform. According to Schulze and Liebner, pyrojapaconitine is identical with pyraconitine.[1]

When pyrojapaconitine is warmed in alkaline solution it undergoes hydrolysis into benzoic acid and *pyrojapaconine*, $C_{25}H_{41}O_8N$. The latter is amorphous, melts at 123°–128°, and has specific rotation, $[\alpha]_D - 73 \cdot 9°$. No crystalline salts have been obtained.

[1] *Arch. Pharm.* 1913, **251**, 453.

Japaconitine is highly toxic, and produces on the heart, respiratory and nervous systems physiological effects similar to, but as a rule slightly greater than, those induced by aconitine (p. 359). Taking the activity of aconitine as equal to unity, that of japaconitine is approximately equal to $1 \cdot 125°$.[1]

Jesaconitine, $C_{40}H_{51}O_{12}N$, was obtained by Makoshi [2] from the roots of a species of aconite, which Miyabe regards as *A. Fischeri*, found in the island of Hokkaido (Jeso) in Japan (p. 353). It is amorphous, and on hydrolysis furnishes benzoic and anisic acids and aconine, the latter identical with that from aconitine, so that it is regarded as benzoylanisoylaconine. It furnishes a triacetyl derivative, m.p. 213°–215°. Its physiological action resembles that of aconitine, but shows certain differences, and it is even more poisonous.

Aconitum Deinorrhizum

Pseudaconitine, $C_{36}H_{51}O_{12}N$, occurs in *Aconitum deinorrhizum*, Stapf, and *A. Balfourii*, Stapf,[3] and is obtainable from " Nepaul aconite roots," which occasionally appear in European commerce. It was first isolated by Wright and Luff,[4] and has since that time been further examined by Dunstan and Carr,[5] Freund and Niederhofheim,[6] and E. Schmidt.[7] It may be prepared by the method described under aconitine. The alkaloid crystallises from chloroform, on adding ether and light petroleum, in colourless rhombs, m.p. 211°–212°. It is readily soluble in alcohol or chloroform, less so in ether, and slightly soluble in water ; its solutions are dextrorotatory, $[\alpha]_D + 18° 36'$ in alcohol. The salts crystallise well and are lævorotatory in solution ; the hydrobromide, $B.HBr.2H_2O$, forms rosettes of colourless cubes, m.p. 191°, $[\alpha]_D - 19 \cdot 5°$ in water ; the hydriodide, $B.HI$, minute needles, m.p. 215°, and the nitrate, $B.HNO_3.H_2O$, needles, m.p. 192° ; the aurichloride, $B.HAuCl_4$, crystallises in golden-yellow needles, m.p. 235°–236°. Pseudaconitine, like aconitine, causes an intense tingling when even a very dilute solution is applied to the tip of the tongue. It also yields a crystalline permanganate which is more stable and somewhat more soluble in water than that of aconitine (*see* p. 359).

[1] Cash and Dunstan, *Phil. Trans.* 1902, **195**, 39.
[2] *Arch. Pharm.* 1909, **247**, 251.
[3] *Bull. Imp. Inst.* 1906, **4**, 37.
[4] *Journ. Chem. Soc.* 1878, **33**, 151.
[5] *Proc. Chem. Soc.* 1895, p. 154 ; *Trans. Chem. Soc.* 1897, **71**, 350.
[6] *Berichte*, 1896, **29**, 852.
[7] *Arch. Pharm.* 1909, **247**, 240.

Pseudaconitine contains six methoxyl groups. When hydrolysed by heating neutral solutions of its salts in water at 135° it undergoes partial hydrolysis into acetic acid and VERATROYLPSEUD-ACONINE, $C_{34}H_{49}O_{11}N.H_2O$. This base crystallises from ether in large irregular crystals, melts at 199°, and is soluble in alcohol, ether, or chloroform, but almost insoluble in water or petroleum. The alkaloid, unlike the parent base, is lævorotatory in solution, $[\alpha]_D - 38 \cdot 15°$ in alcohol. The salts crystallise well; the hydrobromide, $B.HBr.3H_2O$, from alcohol on addition of ether, in large prisms; the nitrate, $B.HNO_3$, in rosettes of rhombic prisms, sinters at 222°, and melts completely at 232°. The aurichloride, $B.HAuCl_4$, is amorphous. When veratroylpseudaconine is allowed to stand with alcoholic sodium hydroxide it is hydrolysed, forming veratric acid and PSEUDACONINE, $C_{25}H_{41}O_8N$. The latter is an amorphous, hygroscopic base, readily soluble in water, chloroform, alcohol, or acetone, and nearly insoluble in ether, but readily combines with alcohol (1 mol.), forming a well-crystallised compound, m.p. 94°–95°, which can be utilised for its isolation in a pure state. It is dextrorotatory, $[\alpha]_D + 39 \cdot 11°$ in water. The salts, owing to their deliquescent nature, are difficult to obtain crystalline, but the aurichloride, $B.HAuCl_4$, has been obtained in needles, m.p. 125°–126°.[1]

When pseudaconitine is heated at its melting-point it loses a molecule of acetic acid, forming *pyropseudaconitine*, a colourless varnish, insoluble in water, but readily soluble in ether, chloroform, or alcohol. The hydriodide forms colourless prisms.

Pseudaconitine is intensely poisonous and closely resembles aconitine in physiological action, but is more toxic; if the activity of aconitine is taken as equal to unity, that of pseudaconitine would be from 2·2 to 2·5.[2]

Aconitum Chasmanthum, Stapf

The roots of this species, known in India as "Mohri," were examined by Dunstan and Andrews [3] by a slightly modified form of the process described under aconitine (*see* p. 355), and found to contain the crystalline alkaloid indaconitine.

Indaconitine, $C_{34}H_{47}O_{10}N$, crystallises in rosettes of colourless needles or in hexagonal prisms from ether, the latter form being

[1] Dunstan and Andrews, *Trans. Chem. Soc.* 1905, **87**, 1620.
[2] Cash and Dunstan, *Phil. Trans.* 1902, **195**, 39.
[3] *Trans. Chem. Soc.* 1905, **87**, 1620.

very similar to, and possibly isomorphous with, aconitine. It has m.p. 202°–203°, and $[\alpha]_D + 18°\ 17'$ in alcohol. The hydrobromide separates from water in hexagonal prisms, m.p. 183°–187° (*dry*), $[\alpha]_D - 17°\ 16'$, or from alcohol by addition of ether in crystals, m.p. 217°–218° ; the aurichloride, $B.HCl.AuCl_4$, crystallises from hot alcohol in rosettes of yellow needles, sinters at 142°, and melts at 147°–152° ; it exists in one form only, but crystallises from chloroform on addition of ether with 1 mol. of chloroform. Like aconitine, indaconitine causes an intense tingling when even a very dilute solution is applied to the tip of the tongue, and gives a crystalline precipitate with permanganate, but the crystals are smaller. It contains four methoxyl groups. When indaconitine sulphate in aqueous solution is heated in a sealed tube it undergoes hydrolysis, yielding 1 mol. each of acetic acid and BENZOYLPSEUDACONINE (indbenzaconine). The latter is a colourless varnish, m.p. 130°–133°, $[\alpha]_D + 33°\ 35'$ (in alcohol), yielding well-crystallised lævorotatory salts ; the hydrobromide, $C_{32}H_{45}O_9N.HBr.2H_2O$, m.p. 247° (*dry*), crystallises in rosettes ; the hydrochloride forms needles or octahedra, m.p. 242°–244° (*dry*), $[\alpha]_D - 8·0°$ in water, and the aurichloride crystallises from alcohol in orange-coloured rosettes, m.p. 180°–182°, but when recrystallised from alcohol by addition of light petroleum is partly converted into aurichlorindbenzaconine, m.p. 234°–235°, which forms minute colourless needles, and is unstable in the light. When indaconitine is allowed to stand at atmospheric temperature with alcoholic soda it is hydrolysed, forming 1 mol. each of acetic acid, benzoic acid, and PSEUDACONINE, $C_{25}H_{41}O_8N$, the latter being identical with the final basic product of the hydrolysis of pseudaconitine (*see* p. 365).

When indaconitine is heated at its melting-point it loses 1 mol. of acetic acid and furnishes a new base, α-*pyroindaconitine*, $C_{32}H_{43}O_8N$, which is amorphous, but yields a crystalline hydrobromide, m.p. 194°–198° (*dry*), which is dextrorotatory like the free base ; the aurichloride is amorphous. Indaconitine hydrochloride, heated at 165°–170° for a few minutes, yields the isomeric β-*pyroindaconitine*, which is also amorphous, but gives a crystalline hydrobromide (small needles, m.p. 248°–250°, $[\alpha]_D + 27°\ 37'$).

Indaconitine and its salts are highly poisonous and in general exert a physiological action differing only in degree from that of aconitine (*see* p. 359). The poisonous dose is similar to that for aconitine. As is the case with the aconitines as a class, the toxicity disappears with the removal of the acetyl group and benzoylpseud-

PLATE VI.

FIG. 1.

FIG. 2.

INDIAN ACONITES.

FIG. 1.—*Aconitum spicatum.*   FIG. 2.—*Aconitum laciniatum.*

aconine (indbenzaconine), like benzaconine, is scarcely poisonous. The physiological action of pseudaconine from indaconitine resembles that of aconine (p. 360) and of pseudaconine from pseudaconitine (p. 365).[1]

Aconitum Spicatum, Stapf

This species is one of those known in India as " bikh " or " bish," and it has been suggested that it yields the " Nepaul aconite " of European commerce, though this is unlikely in view of the fact that " Nepaul aconite " contains pseudaconitine, which is quite distinct from the bikhaconitine found in *A. spicatum* roots. The roots of this species were examined by Dunstan and Andrews.[2]

Bikhaconitine, $C_{36}H_{51}O_{11}N . H_2O$, may be obtained from *A. spicatum* roots by the process described under aconitine (p. 355). It crystallises less easily than the aconitines as a class, but may be obtained from ether in button-shaped masses, m.p. 118°–123°, or, better, with $1H_2O$ from alcohol, on addition of water, in colourless granules, m.p. 113°–116° (*dry*), $[\alpha]_D^{20} + 12 \cdot 21°$, in alcohol. It is readily soluble in alcohol, ether, or chloroform, but almost insoluble in water or light petroleum. The salts crystallise well ; the hydrobromide, $B . HBr . 5H_2O$, m.p. 173°–175° (*dry*), $[\alpha]_D^{20} - 12 \cdot 42°$; the hydrochloride, $B . HCl . 5H_2O$, m.p. 159°–161° (*dry*), $[\alpha]_D^{20} - 8 \cdot 86°$, may be crystallised from alcohol on adding ether. The aurichloride, $B . HCl . AuCl_3$, m.p. 232°–233°, separates from chloroform on addition of light petroleum in canary-yellow needles. Bikhaconitine and its salts, even in very dilute solutions, excite the intense tingling sensation characteristic of the aconitines when applied to the tip of the tongue. Bikhaconitine contains six methoxyl groups, of which two are in the veratroyl radical (*see below*).

When an aqueous solution of bikhaconitine sulphate is heated at 130°, hydrolysis takes place with the formation of 1 mol. each of acetic acid and a new base, VERATROYLBIKHACONINE, $C_{34}H_{49}O_{10}N$, m.p. 120°–125°, $[\alpha]_D^{20} + 29 \cdot 9°$, which is amorphous and is best obtained pure by regeneration from the recrystallised aurichloride, $B . HCl . AuCl_3$, which separates from alcohol in clusters of orange-yellow prisms containing $2C_2H_5OH$ or $5H_2O$, m.p. 145°–148° (*dry*). The hydriodide, m.p. 189°–190° (*dry*), forms rosettes of needles from water. The other haloid salts are amorphous.

By the action of alcoholic soda on veratroylbikhaconine at

[1] Cash and Dunstan, *Proc. Roy. Soc.* 1905, B, **76**, 468.
[2] *Trans. Chem. Soc.* 1905, **87**, 1636.

atmospheric temperature, 1 mol. each of veratric acid and BIKH-
ACONINE are formed. Bikhaconine, $C_{25}H_{41}O_7N$, is amorphous,
$[\alpha]_D^{22} + 33.85°$, and differs from its analogues aconine (p. 358),
japaconine (p. 363), and pseudaconine (p. 365) in being soluble in
ether and in yielding readily crystallisable salts ; the hydrobromide,
B.HBr, m.p. 145°–150° (dry), forms tetragonal prisms ; the nitrate,
B.HNO$_3$.2H$_2$O, m.p. 125°–128°, $[\alpha]_D^{20} + 15.38°$, separates from
alcohol or water in transparent tetragonal prisms with acicular or
pyramidal ends ; the aurichloride, B.HCl.AuCl$_3$.3H$_2$O, m.p. 129°–
132° or 187°–188° (dry), forms glistening rhombic plates on adding
light petroleum to its solution in chloroform or alcohol.

When heated at 180° bikhaconitine loses 1 mol. of acetic acid
and forms PYROBIKHACONITINE, $C_{34}H_{47}O_9N$, a colourless varnish
yielding only amorphous salts ; the aurichloride is yellow and melts
indefinitely at 115°–123°.

Bikhaconitine resembles the " aconitines " generally in physio-
logical action, but agrees most closely with pseudaconitine (p. 365),
and in toxicity lies between japaconitine and pseudaconitine, the
last-mentioned being the most toxic of the three. Bikhaconine
closely resembles aconine, its physiological action being essentially
curare-like in character.[1]

Aconitum Septentrionale

The existence of a toxic crystalline alkaloid in this plant was first
made known by von Schroff in 1871, but it was not until 1896 that
this was isolated and characterised by Rosendahl along with two
amorphous alkaloids. To these three alkaloids he assigned the
following names and formulæ : lappaconitine $C_{34}H_{48}O_8N_2$, septen-
trionaline $C_{31}H_{48}O_9N_2$, and cynoctonine $C_{36}H_{55}O_{13}N_2$. The alkaloids
of the plant have been re-examined recently and almost simul-
taneously by Schulze and Ulfert,[2] and by Weidemann,[3] whose
results differ in important points.

Lappaconitine, $C_{32}H_{44}O_8N_2$,[2] or $C_{32}H_{42}O_9N_2$,[3] crystallises from
alcohol in hexagonal tablets, m.p. 213.5°–214.5°,[2] 223°,[3] $[\alpha]_D + 22.3°$
(in benzene),[2] $+ 27.0°$ (in chloroform),[3] sparingly soluble in cold
alcohol or benzene, easily in chloroform and almost insoluble in water
or ether. No crystalline salts have been prepared. The alkaloid con-
tains two methoxyl groups and a methylimino group according to

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[1] Cash and Dunstan, *Proc. Roy. Soc.* 1905, B, **76**, 468.
[2] *Arch. Pharm.* 1922, **260**, 230.
[3] *Arch. Exp. Path. Pharm.* 1922, **95**, 166.

Schulze and Ulfert, whilst Weidemann found three methoxyl groups. On boiling with dilute sulphuric acid in a current of hydrogen the alkaloid is hydrolysed into acetic acid and PICROLAPPACONITINE [1] (anthranoyllappaconine, $C_{30}H_{42}O_7N_2$. The latter crystallises from alcohol in thick, rhombic tablets, colourless when thin, but showing a slight yellow tint in thick crystals, m.p. (not recorded), $[\alpha]_D^{25} + 22\cdot07°$ (in benzene). The platinichloride, $B.H_2PtCl_6.4H_2O$, forms brownish needles or leaflets, m.p. $300°–310°$ (decomp.). On hydrolysis by hot 10 per cent. alkali, lappaconitine yields LAPPACONINE, $C_{23}H_{37}O_6N.1\frac{1}{2}H_2O$ [1] or $C_{23}H_{35}O_7N.2H_2O$,[2] which is crystalline, m.p. $96°$,[1] $93°$,[2] $[\alpha]_D^{25} + 16\cdot29°$ [1] (in alcohol); $+ 22\cdot41°$ (in alcohol),[2] strongly alkaline and yields well-crystallised salts ; hydrochloride, $B.HCl$, m.p. $246°–247°$,[1] $240°$; [2] aurichloride,[1] $B.HAuCl_4.H_2O$, m.p. $126°–127°$. The acid hydrolytic products of lappaconitine, according to Schulze and Ulfert are anthranilic and acetic acids, whilst Weidemann, who used cold alkali, obtained only one acid, viz., acetylanthranilic acid (lappaconitic acid) which would seem to imply that only one $-$ OH group is engaged with an acyl group in lappaconitine. These results, conflicting though they are, agree in showing that lappaconitine is distinct from lycaconitine, the alkaloid of *Aconitum lycoctonum*, a plant with which *A. septentrionale* is liable to be confused.[3]

Septentrionaline, $C_{33}H_{46}O_9N_2$,[4] has only been obtained in an amorphous condition, $[\alpha]_D^{19\cdot5} + 32\cdot7°$ in alcohol, m.p. $131°$. Weidemann states that it contains four methoxyl groups, and on hydrolysis by alkalis yields (1) a crystalline acid, $C_8H_9O_3N$, m.p. $125°–126°$, which on further treatment with alkali yields anthranilic acid, $C_7H_7O_2N$, and must be a near relative of the latter ; and (2) a basic product, $C_{25}H_{39}O_7N$, m.p. $89°$, $[\alpha]_D^{19\cdot5} + 29\cdot55°$ in alcohol, which is amorphous, but yields a crystalline hydrochloride.

Cynoctonine, $C_{36}H_{55}O_{13}N_2$, is amorphous and dextrorotatory.

Physiological Action. Lappaconitine is stated to possess the typical action of the aconitine group of alkaloids, and paralyses the heart and respiration. Septentrionaline is said to exert a local anæsthetic action and to resemble curare in its effects when in-

[1] *Arch. Pharm.* 1922, **260,** 230.

[2] *Arch. Exp. Path. Pharm.* 1922, **95,** 166.

[3] On the authority of Dr. O. Stapf, Carr has suggested that the *A. Septentrionale*, Koelle, used by Rosendahl (and by Schulze and Weidemann), was probably the true *A. lycoctonum* L, whilst the *A. lycoctonum* referred to on p. 370 is really *A. vulparia*, Reichb.

[4] *Arch. Exp. Path. Pharm.*, 1922, **95,** 166.

jected subcutaneously. Cynoctonine is said to produce convulsions on injection, but, like septentrionaline, is not toxic when swallowed.

Aconitum Lycoctonum [1]

From the roots of this species, Hubschmann isolated the amorphous alkaloids acolyctine and lycoctonine.[2]   Subsequently Dragendorff and Spohn showed [3] that Hübschmann's alkaloids were probably decomposition products of *lycaconitine*, $C_{27}H_{34}O_6N_2.2H_2O$, which they isolated along with *myoctonine*, $C_{27}H_{30}O_8N_2.5H_2O$. These results have been considerably extended by Schulze and Bierling [4] from whose paper the following data are chiefly taken.

Lycaconitine, $C_{36}H_{46}O_{10}N_2$, $[\alpha]_D^{20} + 42 \cdot 5°$ in alcohol, is amorphous and colourless, readily soluble in alcohol or chloroform, less so in ether, weakly basic, and has so far yielded no crystalline derivatives.   On hydrolysis by water or dilute hydrochloric acid it yields succinic acid and ANTHRANOYLLYCOCTONINE, whilst alkalis hydrolyse it to lycoctonic acid (succinylanthranilic acid, $COOH . C_6H_4 . NH . CO . CH_2 . CH_2 . COOH$), m.p. 179°, bright brown needles or leaflets, and LYCOCTONINE, $C_{25}H_{39}O_7N . H_2O$, m.p. 131°–133°, $[\alpha]_D^{20} + 49 \cdot 64°$ in alcohol, long needles from dilute alcohol.   This substance yields crystalline salts with acids (B.HCl.H₂O, m.p. 75° : B.HBr.2H₂O, m.p. 88°–89° ; methiodide, B.MeI, m.p. 178°, pale yellow needles) ; and contains four methoxyl groups, one methylimino group and two hydroxyl groups.

Anthranoyllycoctonine, $C_{32}H_{44}O_8N_2$, is also crystalline, m.p. 154°–155°, and yields a crystalline perchlorate, $B.2HClO_4$, m.p. above 235°.   On hydrolysis by alkalis the base yields lycoctonine and anthranilic acid ;   it is probably identical with Dragendorff's "lycaconine."

Myoctonine $(C_{36}H_{42}O_{10}N_2)_2$, $[\alpha]_D^{20} + 44 \cdot 7°$ in alcohol, the second alkaloid of *A. lycoctonum* is also amorphous, and on hydrolysis by acids furnishes the same products as lycaconitine.

A third unnamed base distinguished by giving an insoluble thiocyanate is present ; on hydrolysis by alkalis it also yields lycoctonine and lycoctonic acid.

According to Hildebrandt,[4] lycaconitine stills the frog's heart in

[1] *A. vulparia ? see* footnote, p. 369.
[2] *Jahresberichte*, 1866, p. 483.
[3] *Pharm. Zeit. für. Russland*, 1884, **23,** 313.
[4] *Arch. Pharm.* 1913, **251,** 8, with a bibliography and critical *résumé* of early work.

five hours in doses of 0·01 grm. and myoctonine in seven hours, death occurring three hours later in each case. Lycoctonine causes paralysis after seven hours, but does not still the heart, whilst the action of the relatively insoluble anthranoyllycoctonine only becomes apparent after seven days. When doses are so reduced as not to paralyse the heart, all the alkaloids show the typical action of the aconitines.

Aconitum Paniculatum, Lam.

According to Brunner,[1] this species contains PANICULATINE, $C_{29}H_{35}O_7N$, small rhombic prisms, m.p. 263°.

Aconitum Palmatum

The roots of this Indian species contain a colourless crystalline alkaloid, PALMATISINE, which resembles atisine from *A. heterophyllum* in being bitter and non-poisonous.[2]

Aconitum Heterophyllum

Atisine, $C_{22}H_{31}O_2N$. The roots of the Indian plant *Aconitum heterophyllum* are employed in native medicine as a mild tonic under the name Atis root. It was first investigated in 1873 by Broughton,[3] who isolated from it the alkaloid atisine, to which he ascribed the formula, $C_{46}H_{74}O_5N_2$. Atisine was subsequently investigated by Wasowicz,[4] who showed that it occurred in atis root associated with aconitic acid. He prepared several crystalline salts and suggested for the alkaloid the formula, $C_{46}H_{74}O_4N_2$. The formula, $C_{22}H_{31}O_2N$, now assigned to it, was proposed by Wright,[5] and was subsequently confirmed by Jowett,[6] who more fully investigated the properties of the alkaloid and its salts.

Atisine is a colourless varnish of indefinite melting-point, slightly soluble in water and readily so in alcohol, ether, or chloroform ; it is lævorotatory, $[\alpha]_D - 19·6°$ in water. The salts crystallise well ; the hydrochloride, B.HCl, forms thin rectangular prisms, m.p. 296°, and is dextrorotatory, $[\alpha]_D + 18·46°$; the hydrobromide, B.HBr, has m.p. 273° and $[\alpha]_D + 24·3°$ in water ; the hydriodide, B.HI, crystallises in brilliant rectangular plates, m.p. 279°, $[\alpha]_D + 27·4°$,

[1] *Schweiz. Apoth. Zeit.* 1922, **60,** 357.
[2] *Bull. Imp. Inst.* 1906, **4,** 39.
[3] *Blue Book, Cinchona Cultivation in East India,* 1877, p. 133.
[4] *Arch. Pharm.* 1879, **214,** 193.
[5] *Year Book of Pharmacy,* 1879, 422.
[6] *Trans. Chem. Soc.* 1896, **69,** 1578.

and is slightly soluble in cold water. The aurichloride, $B.HAuCl_4$, is amorphous, but the platinichloride is a yellowish-brown crystalline powder.

When atisine is heated with alkalis or acids it does not suffer hydrolysis, but is converted into an amorphous hydrate, $B.H_2O$. Atisine is not poisonous. Its physiological action has been investigated by Cash and shown to be somewhat similar to that of aconine (p. 360).

ALSTONIA SPECIES

Alstonine, $C_{21}H_{20}O_4N_2.3\frac{1}{2}H_2O$ (Chlorogenine), an amorphous base isolated by Palm from *Alstonia constricta* bark, used in Australia as a febrifuge, was obtained later by Hesse [1] together with the amorphous alkaloids, *porphyrine*, $C_{21}H_{25}O_2N_3$, and *porphyrosine*, and the crystalline base *alstonidine* (needles, m.p. 181°).

The bark of *Alstonia scholaris* (Dita bark), used as a febrifuge in the Philippines was examined in 1875 by Gorup-Besanez,[2] who isolated from it a crystalline alkaloid, and by Jobst and Hesse [3] in the same year and yielded to them the alkaloids *ditamine, echitamine,* and *echitenine,* of which the second was subsequently identified with Merck and Harnack's ditaine (*see below*). Jobst and Hesse's results were largely confirmed by Bacon.[4] Hesse subsequently found the same three alkaloids in *Alstonia spectabilis* bark and assigned formulæ to them.[5]

Ditamine, $C_{16}H_{19}O_2N$, is an amorphous powder which melts at 75°; its solutions are bitter and strongly alkaline in reaction.

Echitamine, $C_{22}H_{28}O_4N_2.H_2O$ (Ditaine), was obtained as a crystalline tetrahydrate by spontaneous evaporation of its alcoholic solution. This at 80° loses $3H_2O$, giving a crystalline monohydrate, m.p. 206°, $[\alpha]_D - 28\cdot8°$ (in alcohol), which on drying at 105° yields the anhydrous base as a varnish. The monohydrate is soluble in ether or chloroform when freshly precipitated, but almost insoluble when crystallised; it is insoluble in benzene. The hydrochloride, $C_{22}H_{28}O_4N_2.HCl$, is sparingly soluble in water, crystallises in prisms, and melts at 290°, $[\alpha]_D - 57°$ (in water). The platinichloride, $(B.HCl)_2.PtCl_4.3H_2O$, is amorphous. The alkaloid dissolves in concentrated sulphuric acid with a purple-red colour, and gives with

[1] *Annalen,* 1880, **205**, 360.
[2] *Ibid.* 1875, **176**, 88.
[3] *Ibid.* 1875, **178**, 49.
[4] *Philippine Journ. Sci.* 1906, **1**, 1007.
[5] *Annalen,* 1880, **203**, 147, 162.

concentrated nitric acid a fugitive red passing into intense green. Echitamine paralyses the motor nerves in warm-blooded animals and lowers the blood-pressure.[1] The minimum lethal dose for a guinea-pig is about 0·025 grm. per kilogramme of body weight.

Echitenine, $C_{20}H_{27}O_4N$, a brown, amorphous, bitter substance melting above 120°, forms anhydrous amorphous salts and gives colour reactions with nitric and sulphuric acids similar to those of echitamine.

Alstonamine occurs only in the bark of *Alstonia spectabilis*. It is crystalline, but its composition is unknown.

AMANITA MUSCARIA

Muscarine was first detected in fly agaric (*Amanita muscaria*) by Schmiedeberg and Koppe in 1869,[2] who obtained it in the form of a deliquescent syrupy base, exhibiting powerful pharmacological action, arresting the frog's heart in diastole and being antagonised by atropine. Further examination of this base by Harnack,[3] showed that it contained choline, which was eliminated as far as possible as the aurichloride, $C_5H_{14}ON.AuCl_4$, leaving a more soluble aurichloride, which on analysis gave figures corresponding with the formula, $C_5H_{14}O_2N.AuCl_4$. To this alkaloidal chloride Harnack and Schmiedeberg assigned the formula, $(CH_3)_3NCl.CH_2.CH(OH)_2$, which is that of a hydrate of the aldehyde corresponding to choline.

$$(CH_3)_3N(OH).CH_2.CH_2OH \rightarrow (CH_3)_3.N(OH).CH_2CHO \rightarrow (CH_3)_3N(OH).CH_2.CH{\Large<}^{OH}_{OH}$$

Choline 　　　　　　*Betaine aldehyde* 　　　　　　*Hydrated Betaine aldehyde*
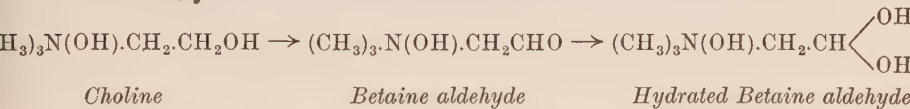
This view seemed to be supported by the observation that choline on treatment with nitric acid yielded a product having a pharmacological action similar to that of muscarine as known up to that time.[4] Careful comparison of the " natural " and " artificial " products by Böhm,[5] however, showed that the former was much

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[1] Harnack, *Berichte*, 1878, **11**, 2004 ; 1880, **13**, 1648 ; Hesse, *ibid.* 1880, **13**, 1841.

[2] *Das Muscarin*, Leipzig, 1869. *Cf. Jahresb.* 1870, p. 875. According to Honda (*Arch. exp. Path. Pharm.* 1911, **65**, 454), muscarine is also present in toadstools, together with two other alkaloids, a- and β-myketosines.

[3] *Arch. exp. Path. Pharm.* 1875, **4**, 168.

[4] *Ibid.* 1876, **6**, 101.

[5] *Ibid.* 1885, **19**, 60. *Cf.* Honda, *ibid.* 1911, **65**, 454 ; Meyer, *Berichte*, 1893, **26**, 801.

more active than the latter and that its action was antagonised by atropine, whilst the " artificial muscarine " had a curare-like action on the atropinised frog. Somewhat later Nothnagel [1] investigated the action of nitric acid on choline and isolated and described the " artificial muscarine " as well as a choline nitrous ester, $(CH_3)_3NCl$. $CH_2 . CH_2 . ONO$, produced in this reaction. The latter is interesting in view of Ewins's [2] more recent investigation, the results of which show that " artificial muscarine " (now also called by various workers, synthetic muscarine, choline-muscarine, pseudo-muscarine), is choline nitrous ester, and Dale,[3] working with Ewins's material, showed that it had all the pharmacological properties attributed to " artificial muscarine." Several other attempts have been made [4] by the synthesis of bases having the formula, $C_5H_{14}O_2NCl$, to clear up the question. Recently H. King [5] succeeded in isolating from fly agaric in a pure state a base having in a much enhanced degree the pharmacological action characteristic of the substance originally obtained in Schmiedeberg's laboratory and having a molecular weight considerably higher than that of choline, and representing, therefore, a more complex substance, which can probably be definitely classed with the alkaloids.

King isolated muscarine by macerating fresh fly agaric in alcohol, distilling the solvent from the extract under reduced pressure (temp. below 50°), and separating oil and fat from the residual extract by means of ether. In this way the muscarine content (0·4 grm. as determined by physiological assays) of 25·5 kilos of fresh fungus was obtained in 2·25 litres of aqueous extract (A), which was then further concentrated to a thick syrup and this thoroughly extracted with successive portions of absolute alcohol (the complete removal of the muscarine by absolute alcohol was controlled by physiological tests with reference to a portion of (A), diluted, sterilised and kept for use as a standard). This first alcoholic extract was concentrated, the viscous syrup re-exhausted with absolute alcohol, and this in turn concentrated to a thick product, which was dissolved in 500 c.c. of water and treated with

[1] *Berichte*, 1893, **26,** 801 ; *Arch. Pharm.* 1894, **232,** 286.

[2] *Bio-chem. Journ.*, 1914, **8,** 209. *Cf.* Weinhagen, *J. Amer. Chem. Soc.* 1920, **42,** 1670.

[3] *J. Physiol.* 1914, **48,** 24.

[4] *See*, for example, Schmidt and Bode, *Annalen*, 1892, **267,** 268 ; Ewins, *Bio-chem. Journ.*, 1914, **8,** 366; (pharmacological) Dale, *J. Pharm. Expt. Ther.* 1914, **6,** 147.

[5] *Trans. Chem. Soc.* 1922, **121,** 1743.

837 c.c. of colloidal iron solution (5 per cent. Fe_2O_3), and the filtrate, after concentration to 400 c.c., treated with basic lead acetate. The filtrate from this, after deleading, was concentrated to a syrup, and this again exhausted with absolute alcohol. The concentrate from this was dissolved in water and the choline and muscarine obtained from it in four fractions by precipitation with (1) mercuric chloride in water ; (2) mercuric chloride in alcohol ; (3) mercuric chloride in alcohol after removal of sodium acetate, which was found to inhibit the precipitation of the mercurichlorides ; (4) phosphotungstic acid in 5 per cent. sulphuric acid. This left an inactive filtrate. Precipitates (1) and (2), which contained respectively about 14 and 34 per cent. of the muscarine originally present were demercurated and the bases present converted first into chlorides, then into carbonates, and the latter into d-hydrogen tartrates, of which the choline salt is the less soluble, and the bulk of the choline was removed in that way by concentrating the aqueous solution to a thin syrup and adding a large volume of hot absolute alcohol,[1] the process being repeated until physiological tests showed that the whole of the muscarine remained in the uncrystallisable syrup. The contents of the latter were then converted from tartrates to chlorides and the fractionation continued with gold chloride, choline aurichloride being less soluble than the muscarine salt which accumulated in the later oily fractions and the ultimate mother liquors. From these it eventually separated in pale yellow nodules or aggregates, which could be picked out mechanically, and after being recrystallised twice from dilute acid containing a little gold chloride, yielded glistening delicate leaflets of muscarine aurichloride containing 38·2 (*mean*) per cent. of gold, corresponding to a molecular weight of about 210 for the free base. The total weight of pure aurichloride obtained amounted to 0·12 grm. Of the pure muscarine chloride made from this aurichloride, only 1/500 mg. was required to stop the frog's heart in diastole, as against 1/20 to 1/30 mg. recorded by Schmiedeberg and Harnack. King also compares the behaviour of choline and muscarine with various alkaloidal precipitants.

In addition to natural muscarine and the so-called artificial synthetic or pseudo-muscarine (choline nitrite) referred to in the foregoing summary, two other products are of interest in this connection, since their names suggest a connection with muscarine, viz. : (1) *iso*MUSCARINE, $(CH_3)_3N(OH).CHOH.CH_2OH$, which was pre-

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[1] *Cf.* Honda, *Arch. exp. Path. Pharm.* 1911, **65,** 454.

pared by Bode,[1] and shown to be toxic, but distinct from muscarine in physiological action ; and (2) ANHYDROMUSCARINE (betaine aldehyde), $(CH_3)_3N(OH).CH_2.CHO$, made first by Berlinerblau [2] and later by Fischer,[3] and which differs from both " natural " and " artificial " muscarine in having practically no action on the frog's heart.

ARISTOLOCHIA SPECIES

A considerable number of species of *Aristolochia* have been used in medicine in various parts of the world ; at the present time the stems and roots of *Aristolochia indica* and *A. bracteata* are so used in India, and under the name of serpentary the rhizomes and roots of *A. Serpentaria*, Lam., and *A. reticulata*, Nutt, are so employed in the United Kingdom and the United States. These are all now used as bitter tonics, but all four have in the past enjoyed an unfounded reputation as remedies for snake bites. They all contain bitter substances, and Hesse suggested [4] that the bitter substance isolated by Chevallier from *A. reticulata* may contain some aristolochine (*see below*), but it is not yet certain that any of these species contain alkaloids.[5] In *A. longa*, Hesse [4] was unable to find any alkaloidal constituents.

The three species which have been fully investigated are *A. Clematitis*, *A. rotunda* and *A. argentina*, all occurring in South America.

Aristolochine (*Aristolochic acid*, Hesse), $C_{32}H_{22}O_{13}N_2$ or $C_{17}H_{11}O_7N$, was isolated by Pohl [6] from the seeds of *A. Clematitis* and the roots of *A. rotunda*. It forms orange-yellow needles, decomposes at 215°, is soluble in ether, alcohol, boiling water, or alkaline solutions, and dissolves in concentrated sulphuric acid with a dark green colour. The alkaloid is highly poisonous, especially when injected intravenously, causing dilatation of the blood-vessels in the intestinal tract, resulting in a fall in blood-pressure and sometimes hæmorrhage.

From the root of the allied species *Aristolochia argentina*, Hesse [4] has obtained the following series of alkaloids :

Aristinic acid, $C_{18}H_{13}O_7N$, crystallises from hot acetic acid

[1] *Annalen*, 1892, **267**, 268.
[2] *Berichte*, 1884, **17**, 1139.
[3] *Ibid.* 1893, **26**, 464.
[4] *Pharm. Journ.* 1891–92, **51**, 551.
[5] *Cf.* Dymock, Warden and Hooper, *Pharmacographia indica*, 1893, vol. iii, p. 163.
[6] *Arch. f. exp. Path.* 1891, **29**, 282. *Cf.* Hesse, *Arch. Pharm.* 1895, **233**, 684.

in greenish-yellow leaflets or needles, m.p. 275° (*decomp.*). The potassium salt, $C_{18}H_{12}O_7NK.2H_2O$, separates from potassium hydroxide solution in reddish needles ; the methyl ester forms yellow needles, m.p. 250°.

Aristidinic acid, $C_{18}H_{13}O_7N$, is isomeric with the foregoing : it forms greenish-yellow needles, m.p. 260° (*approx.*), and contains one methoxyl group.

Aristolic acid, $C_{15}H_{11}O_7N$, forms orange-red needles, m.p. 260°–270°, and, like the two foregoing alkaloids, gives a green solution with concentrated sulphuric acid.

From the same source Hesse obtained [1] an amorphous alkaloid which he called " aristolochine," and which was different from Pohl's aristolochine. The latter he proposed should be named aristolochic acid, and suggested that it was probably a lower homologue of aristinic or aristolic acid.

ASPIDOSPERMA SPECIES

The two species of this genus which have been examined are *Aspidosperma Quebracho*, Schlecht, from Argentina, and an unidentified species from Central America, which yields the so-called " Payta " bark. *A. Quebracho* is sometimes confused with the quebracho of the Argentine, which yields the quebracho wood of commerce largely used for making the tanning extract of the same name and derived from a different species, *Quebrachia (Loxopterygium) Lorentzii*, Griseb (p. 443). The latter bears the local name " quebracho colorado," and the former is called " quebracho blanco." Quebracho blanco bark is used in South America as a substitute for cinchona in the treatment of fevers and malaria. It was examined by Fraude,[2] who isolated from it the alkaloid aspidospermine, and later by Hesse,[3] who isolated five other bases of which only one, quebrachine, was well enough characterised to be found by later investigators. Quebrachine was shown by Fourneau and Page [4] to be identical with yohimbine (p. 392), and this has been confirmed by Ewins,[5] and accepted by Barger and Field. Ewins, in the course of an investigation of aspidospermine, isolated two other alkaloids, which have not been named. One crystallises from ethyl acetate

[1] *Pharm. Journ.* 1891–92, **51,** 551.
[2] *Berichte,* 1878, **11,** 2189 ; 1879, **12,** 1560.
[3] *Annalen,* 1882, **211,** 249.
[4] *Bull. Sci. Pharmacol.* 1914, **21, 7.**
[5] *Trans. Chem. Soc.* 1914, **105,** 2738.

in octahedra, m.p. 176°–177°, is sparingly soluble in chloroform, and gives no colour reactions with oxidising agents. The other is sparingly soluble in ether, crystallises from light petroleum in stout prisms, m.p. 149°–150°, and gives colour reactions similar to but less intense than those of aspidospermine. Hesse's alkaloids, aspidosamine, aspidospermatine, m.p. 162°, $[\alpha]_D - 73 \cdot 3°$, hypoquebrachine and quebrachamine, m.p. 142°, need not be further described. The first and third Ewins suggests are decomposition products of aspidospermine.

Aspidospermine, $C_{22}H_{30}O_2N_2$, crystallises from alcohol or light petroleum in needles, m.p. 208°, b.p. 220°/1–2 mm., $[\alpha]_D^{18} - 99°$ (in alcohol), $- 93°$ (in chloroform), is fairly readily soluble in organic solvents, but almost insoluble in water. It is feebly basic and does not form crystalline salts. It dissolves unchanged in cold sulphuric acid, but addition of potassium dichromate produces a brown coloration changing to green : perchloric acid gives a rose-red colour. The alkaloid contains one methoxyl group, and no evidence of a methylimino group could be got by the Herzig-Meyer method but the residue from this reaction contains a new base, ASPIDOSINE, $C_{19}H_{26}ON_2$, which crystallises from alcohol or xylene in rectangular prisms or plates, m.p. 236°–244·5°, $[\alpha]_D - 16°$ in alcohol, and gives intense colour reactions, rose-red with sulphuric acid, greenish-blue with ferric chloride, and deep orange-red with sulphuric followed by nitric acid. The hydriodide, B.HI, is sparingly soluble in cold, but readily in hot water from which it crystallises in cubes and octahedra, m.p. above 280°. When boiled with dilute hydrochloric acid, aspidospermine evolves one molecule of acetic acid forming DEACETYLASPIDOSPERMINE, $C_{20}H_{28}ON_2$, which crystallises from acetone in long prismatic needles, m.p. 110°–111°, b.p. 210°/1–2 mm., $[\alpha]_D + 2 \cdot 8°$ in dry alcohol. In sulphuric acid solution it gives with nitric acid a violet, with potassium dichromate a deep brownish-purple colour, and with ferric chloride a deep magenta tint. The hydriodide, B.HI, crystallises from hot dilute hydriodic acid in rectangular prisms, m.p. 235°–243°, and is very sparingly soluble in cold water. The benzoylderivative forms stout rhombs, m.p. 186°–187° from alcohol, and the dimethiodide, $C_{20}H_{28}ON_2$, octahedra, m.p. 176°–177°. On acetylation the deacetyl base is reconverted into aspidospermine. With nitrous acid it forms a nitronitroso derivative, $C_{20}H_{26}O_4N_4$, m.p. 155°–160° (*decomp.*), which boiling hydriodic acid converts into aspidosine (*see above*).

On oxidation with chromic acid aspidospermine yields a new

base, $C_{15}H_{24}O_2N_2$, crystallising from ethyl acetate in stout prisms, m.p. 192°–193°. On the basis of these results, Ewins suggests that the two oxygen atoms in aspidospermine are present as a methoxyl and a N-acetyl group, that deacetylaspidospermine is a secondary-tertiary base, and that both are derivatives of a reduced quinoline.

Quebrachine. (*See* " Yohimbine," p. 392.)

Physiological Action. The physiological action of the quebracho alkaloids was investigated by Penzoldt,[1] who found that in frogs, aspidospermatine, aspidospermine, hypoquebrachine and quebrachamine act on the central nervous system, producing paralysis of the motor nerves, whilst aspidosamine and quebrachine (*see also* p. 392) produce the same effect in a curare-like manner. In mammals the chief effect is the stimulation of the respiratory centre with small doses, and paralysis with large doses.

Payta bark (*Aspidosperma* sp.). This material, according to Hesse, contains two alkaloids.[2]

Paytamine, $C_{21}H_{24}ON_2$, occurs in the bark in minute amount. The alkaloid is amorphous and distinguished from paytine by not being precipitated by potassium iodide solution.

Paytine, $C_{21}H_{24}ON_2 \cdot H_2O$, also isolated by Hesse, crystallises from alcohol, melts at 156°, $[\alpha]_D$ — 149·5°, dissolves in most organic solvents, but sparingly in water ; the solutions are alkaline in reaction, and possess a bitter taste. The hydrochloride, $B \cdot HCl$, crystallises from hot water in prisms ; with perchloric acid it gives a magenta-red colour.

CALYCANTHUS GLAUCUS

From the seeds of this plant, Eccles,[3] and later Wiley, obtained the alkaloid calycanthine, and this has been further examined, along with its isomeride *iso*calycanthine, which also occurs in the seeds, by Gordin.[4]

Calycanthine, $C_{11}H_{14}N_2 \cdot \frac{1}{2}H_2O$, crystallises in orthorhombic bipyramids, m.p. 216°–218°, or 243°–244° (*dry*), has a bitter taste, is slightly alkaline to litmus, and readily soluble in ether or chloroform. The salts crystallise well. The alkaloid is a secondary-tertiary base, gives a nitrosoamine, m.p. 175°–176° (*decomp.*), and

[1] *Annalen*, 1882, **211**, 271.

[2] Hesse, *Annalen*, 1870, **154**, 287 ; 1873, **166**, 272 ; 1882, **211**, 280.

[3] *Proc. Amer. Pharm. Assoc.* 1888, **84**, 382.

[4] *Journ. Amer. Chem. Soc.* 1905, **27**, 144, 1418 ; 1909, **31**, 1305 1911, **33**, 1626.

contains a $N.CH_3$ group. It resembles strychnine in physiological action.

*iso*Calycanthine, $C_{11}H_{14}N_2.\frac{1}{2}H_2O$, forms orthorhombic crystals, m.p. 212°–214°, or 235°–236° (*dry*), yields a nitrosoamine, m.p. 106°–107° (*decomp.*), and with methyl iodide gives a mixture of the hydriodide with a quaternary iodide, $C_{24}H_{28}ON_3I.H_2O$; the latter forms colourless needles, m.p. 213°–214°. It is suggested that this substance is formed by condensation of two molecules of the alkaloid accompanied by atmospheric oxidation.

CARICA PAPAYA

Carpaïne, $C_{14}H_{25}O_2N$, was obtained by Greshoff [1] from the fruit and seeds, but especially the leaves, of the papaw tree (*Carica Papaya*), and was afterwards investigated by Merck,[2] who assigned to it the formula, $C_{14}H_{27}O_2N$, and later by van Rijn,[3] who prepared a number of its salts and showed that the alkaloid was a secondary base and that it contained a hydroxyl group, but no methoxyl. Carpaïne has been investigated by Barger, who has made some progress in the determination of its constitution.[4] The alkaloid has also been found in *Vascancellea hastata* by Wester.[5]

Carpaïne crystallises in monoclinic prisms, m.p. 121°, b.p. 215°–235° *in vacuo*, $[\alpha]_D + 21° 55'$ in alcohol, is insoluble in water, but soluble in most organic solvents. The hydrochloride, B.HCl, crystallises from water in needles ; the aurichloride, $B.HAuCl_4.5H_2O$, from alcohol in yellow needles, m.p. 205° (*dry*).

Methylcarpaïne, obtained by the action of methyl iodide on the base, forms colourless prisms, m.p. 71°. Nitrosocarpaïne crystallises from alcohol in small prisms, m.p. 144°–145°.

Barger has found that when carpaïne is heated with 10 per cent. hydrochloric acid at 130°–140°, or with sodium ethoxide, it is converted by addition of one molecule of water into carpamic acid, $C_{14}H_{27}O_3N$, long needles, m.p. 224°, from alcohol, on addition of acetone. On oxidation with permanganate in acetone, carpaïne furnishes ammonia and a nitrogenous acid. The latter yields a methyl ester, which on hydrolysis gives ammonia and an acid, $C_8H_{14}O_4$ (possibly α-δ-dimethyladipic acid), which is also produced

[1] *Meded. uit's Lands Plant.*, 1890, No. 7, p. 5.
[2] *Merck's Report*, 1891, p. 30.
[3] *Arch. Pharm.* 1893, **231**, 184 ; 1897, **235**, 332.
[4] *Trans. Chem. Soc.* 1910, **97**, 466.
[5] *Ber. deut. Pharm.* 1914, **24**, 123.

by the direct oxidation of carpaïne by nitric acid. On the basis of the results so far obtained, Barger suggests the following formula as possibly representing carpaïne :

$$CH.CH_3$$

CH$_2$ CH.O.CO
| | >C$_5$H$_{10}$
CH$_2$ CH—NH

$$CH.CH_3$$
Carpaïne
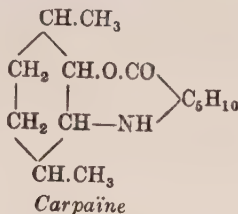
No structure can yet be suggested for the group, C_5H_{10}.

Carpaïne has an intensely bitter taste. According to Plugge, the alkaloid depresses the action of the heart and adversely affects respiration, whilst von Oefele recommends its application by sub-cutaneous injection as a substitute for digitalis in cardiac diseases.

CASIMIROA EDULIS

From the seeds of this Mexican plant Bickern isolated an alka-loidal glucoside, " casimirine," $C_{30}H_{32}O_5N_2$.[1] Power and Callan [2] were unable to confirm the existence of " casimirine," but obtained instead the alkaloids casimiroine and casimiroedine.

Casimiroine, $C_{24}H_{20}O_8N_2$, crystallises from alcohol in rosettes of needles, m.p. 196°–197°, $[\alpha]_D$ 0°, gives an aurichloride, $B.HAuCl_4$, orange-yellow needles, m.p. 195°–196°, and a picrate, m.p. 165°.

It contains two methoxyl groups, and on hydrolysis by boiling alcoholic potash yields CASIMIROITINE, $C_{23}H_{22}O_7N_2$, which crystallises from alcohol in hair-like needles, m.p. 171°, and appears to be formed by the addition of a molecule of water, and the loss of a molecule of carbon dioxide.

Casimiroedine, $C_{17}H_{24}O_5N_2$, crystallises from alcohol in warty masses of small needles, m.p. 222°–223°, $[\alpha]_D$ — 36·5° in dilute hydrochloric acid, and gives an aurichloride, $B.HAuCl_4.2H_2O$, bright yellow microscopic needles, m.p. 90° (*approx.*) or 145°–148° (*dry, decomp.*), which is dissociated by water, but can be recrystal-lised from dilute hydrochloric acid.

Both alkaloids are physiologically inactive.

[1] *Arch. Pharm.* 1903, **241,** 166.
[2] *Trans. Chem. Soc.* 1911, **99,** 1993.

CLAVICEPS PURPUREA (ERGOT)

Ergot consists of the mycelia of *Claviceps purpurea*, a fungus which occurs on grasses and cereal crops, but especially on rye.[1] This material has long been used in medicine,[2] and was first investigated by Wenzell in 1865, who prepared from it two basic products which he named ergotine and ecboline.[3]   A crystalline alkaloid, ergotinine, was obtained from ergot for the first time by Tanret, who also isolated from the mother liquors of this alkaloid an amorphous base which he named " amorphous ergotinine." [4]   Tanret's crystalline ergotinine is probably identical with the " picrosclerotine " of Dragendorff and Podwyssozki,[5] and with Jacobi's " secaline." [6]   Kobert [7] showed that crystallised ergotinine was practically physiologically inactive, whilst the amorphous alkaloid, which he called cornutine, was highly active.   This amorphous alkaloid has been obtained in an impure condition by various investigators, but was obtained pure for the first time by Barger and Carr,[8] who named it ergotoxine.   It was prepared almost simultaneously by Kraft,[9] who called it hydroergotinine, since it is converted into ergotinine by loss of water.   It seems clear that Tanret's " amorphous ergotinine," Kobert's " cornutine," and Jacobi's " sphacelotoxine " were all products whose activity depended on the presence of some ergotoxine.

Quite recently Spiro and Stoll have isolated from ergot a new alkaloid, ergotamine, which has qualitatively and quantitatively the same action as ergotoxine.[10]

Since 1906 a large number of other well-defined products, chiefly amino-acids, have been isolated from ergot, including betaine and choline, putrescine, and cadaverine, some of which are not markedly active physiologically.[11]   The more important of these new constituents are described below.   No completely satisfactory method

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[1] *Cf.* Tanret, *Compt. rend.* 1922, **174,** 827.

[2] For a historical summary of investigations on ergot *see* Barger, *Pharm. Journ.* 1920, November 27, p. 471.

[3] *Amer. Journ. Pharm.* 1864, **36,** 193.

[4] *Compt. rend.* 1875, **81,** 896 ; 1878, **86,** 888.

[5] *Arch. exp. Path. Pharm.* 1876, **6,** 153.

[6] *Ibid.* 1897, **39,** 104.

[7] *Ibid.* 1884, **18,** 316.

[8] *Chem. News,* 1906, **94,** 89.

[9] *Arch. Pharm.* 1906, **244,** 336.

[10] *Verh. Schweiz Nat. Ges.* 1920 ; *Chem. Soc. Abstr.* 1922 [i], 47.

[11] *Cf. e.g.* Fränkel and Rainer, *Biochem. Zeits.* 1916, **74,** 167.

of estimating the physiological activity of ergot or its galenical preparations has yet been devised.

For the isolation of ergotoxine and ergotinine Barger and Carr recommend the following method : [1] The ground ergot is extracted with alcohol, the solvent distilled off, and the residue, after washing with light petroleum to remove oil, is dissolved in ethyl acetate and shaken out with successive quantities of citric acid solution until all the alkaloid has been removed. To the citric acid solution sodium bromide is added, which precipitates a mixture of ergotoxine and ergotinine hydrobromides. When this mixture is shaken with dilute caustic soda and ether, the ergotinine is dissolved by the ether first, and after separation in this way may be crystallised from alcohol. Ergotoxine remains in the mother liquors and is obtained by neutralising these, then making alkaline with sodium carbonate and extracting with ether. The residue left on distilling off the ether is dissolved in 80 per cent. alcohol and a slight excess of phosphoric acid in alcohol added, when ergotoxine phosphate crystallises out after a few days and can be recrystallised from alcohol.

Ergotoxine, $C_{35}H_{41}O_6N_5$ (*Hydroergotinine*), is a bulky white powder, m.p. 162°–164°, soluble in cold alcohol, sparingly so in ether. The specific rotation of specimens prepared by Barger and Carr in several ways varied from $+ 0.6°$ to $+ 40.6°$ in alcohol.

Ergotoxine is precipitated by the usual alkaloidal reagents and is particularly sensitive to Mayer's reagent and to iodine solution, which give precipitates with one part in two million and one million respectively. It forms well-crystallised salts, which are best prepared by adding an alcoholic solution of the appropriate acid to a dilute solution of ergotoxine in ether ; the salts with inorganic acids are sparingly soluble in water. The phosphate, $B.H_3PO_4.H_2O$, forms groups of needles, m.p. 186°–187° (*decomp.*), and is soluble in 14 parts of boiling or 313 parts of cold 90 per cent. alcohol ; with cold water it gives a colloidal solution which on addition of N-hydrochloric acid forms a jelly : the hydrochloride, $B.HCl$, forms minute, diamond-shaped plates, m.p. 205° ; the neutral oxalate, $B_2.H_2C_2O_4$, forms rectangular elongated plates, m.p. 179°, and the acid oxalate, $B.H_2C_2O_4$, minute prisms, m.p. 179° (*decomp.*). Kraft [2] observed that when ergotoxine is boiled with methyl alcohol it is converted into ergotinine, $C_{35}H_{39}O_5N_5$, and Barger and Carr have found that

[1] *Trans. Chem. Soc.* 1907, **91,** 337.
[2] *Arch. Pharm.* 1906, **244,** 336.

the same change occurs when ergotoxine is treated with acetic anhydride and is due to the loss of one molecule of water.

Barger and Ewins [1] have shown that ergotoxine and ergotinine probably contain a methylimino group. Both ergotoxine and ergotinine, when heated dry, yield *iso*butyrylformamide, $(CH_3)_2CH.CO.CO.NH_2$.

Ergotinine, $C_{35}H_{39}O_5N_5$, prepared as described already, crystallises from dry alcohol in long needles, m.p. 229° (placed in a bath at 210°), $[\alpha]_D + 338°$ in alcohol, $+ 396°$ in chloroform, is readily soluble in acetone or chloroform, less so in alcohol (1 in 292 at 18° or 1 in 52 boiling), and sparingly in ether. The salts are all amorphous. Ergotinine is distinctly less sensitive to alkaloidal precipitants than ergotoxine, but Mayer's reagent gives a cloudiness with 1 part in 1,000,000, and iodine solution with 1 part in 200,000. The relationship of ergotinine to ergotoxine has been discussed above. Kraft [2] has observed that ergotinine is partly converted into ergotoxine when allowed to stand in dilute acetic acid. Barger and Ewins [1] have found that when ergotinine in alcohol is heated with phosphoric acid it is converted into ethyl ergotoxine phosphate. Both ergotinine and ergotoxine, dissolved in ether, give with sulphuric acid a transient orange colour changing to blue, whilst a solution in sulphuric acid gives with dry ferric chloride an orange tint changing to crimson, green, and blue. [3]

Ergotamine, $C_{33}H_{35}O_5N_5$. The isolation of this alkaloid was first announced by Spiro and Stoll in 1920, but the first detailed description was given by the latter author in 1922. [4] It was apparently obtained by extracting ergot (mixed with aluminium sulphate to retain the alkaloids) first with ether or benzene to remove oil, and then with ether again after addition of a base to liberate the alkaloid. The second ethereal solution, on removal of the solvent, leaves crystalline ergotamine in a yield of 0·01 to 0·02 per cent. The alkaloid crystallises from acetone, with 2 mols. of acetone and 2 mols. of water, $B.2COMe_2.2H_2O$, in highly refractive prisms, $[\alpha]_D^{20} - 155°$ in 0·6 per cent. solution in chloroform. On heating the alkaloid decomposes at 140°, and at 180° forms a brown mass and evolves gas. When kept in ethylic alcohol solution it is converted into an isomeride *ergotaminine*, which crystallises in triangular leaflets and

[1] *Trans. Chem. Soc.* 1918, **113,** 235.   *Cf.* 1910, **97,** 284.
[2] *Arch. Pharm.* 1906, **244,** 366.
[3] *Cf.* Wolter, *Chem. Zeit.* 1918, **42,** 466.
[4] *Verh. Schweiz Nat. Ges.* 1920 ; *Schweiz Apoth. Zeit.* 1922, **60,** 341.

has $[\alpha]_D^{20} + 381°$ in 0·6 per cent. chloroform solution and is a weaker base than ergotamine. Both alkaloids give a blue coloration with sulphuric acid. Ergotamine, which is a monoacidic base yields crystalline salts by the method described under ergotoxine,[1] viz., addition of the acid to the base dissolved in a solvent such as alcohol or acetone miscible with water, when they separate almost immediately. The hydrochloride forms thin prisms, and the tartrate compact prisms. The salts become brown when exposed to air.

Aminosecalesulphonic acid, $NH_2 . C_{15}H_{27}O_{15} . SO_3H$ (Kobert's ergotic acid), was obtained by Kraft together with betaine and choline. According to Vahlen [2] aminosecalesulphonic acid is physiologically inert.

Clavine. This supposed new physiologically active constituent of ergot, obtained by Vahlen,[3] was shown by Barger and Dale [4] to be a mixture of leucine and aspartic acid and to be physiologically inert.[5]

p-**Hydroxy-β-phenylethylamine** was isolated by Barger [6] by extracting a concentrated aqueous extract of ergot made alkaline with sodium carbonate solution with amyl alcohol, and removing the phenolic amine from this with dilute caustic soda solution. This was then neutralised, evaporated to dryness, and the residue extracted with alcohol. From this solution impurities were precipitated by mercuric chloride, excess of mercury removed by hydrogen sulphide, the filtrate concentrated, made slightly alkaline with caustic soda, and shaken out with ether, which removed no physiologically active substance. The solution after neutralisation was made alkaline with sodium carbonate, and again shaken with ether, which extracted *p*-hydroxyphenylethylamine, identified by means of its dibenzoyl derivative, m.p. 167°. The substance has been synthesised by Barger [7] by the reduction of *p*-hydroxyphenyl-acetonitrile, first prepared by Pschorr, Wolfes and Buckow,[8] with

[1] British Patent 170,302 (*Chem. Soc. Abstr.* 1923 [i], 480).
[2] *Arch. exp. Path. Pharm.* 1908, **60,** 42.
[3] *Ibid.* 1906, **55,** 136.
[4] *Bio-chem. Journ.* 1907, **2,** 240.
[5] *Cf.* Vahlen, *loc. cit.,* and 1908, **60,** 42.
[6] *Trans. Chem. Soc.* 1909, **95,** 1125. It also occurs in American but not in European mistletoe. Crawford and Watanabe, *Journ. Biol. Chem.* 1914, **19,** 303 ; 1916, **24,** 169.
[7] Barger, *loc. cit.* For other syntheses *see* Barger and Walpole, *Trans. Chem. Soc.* 1909, **95,** 1720 ; Rosenmund, *Berichte,* 1909, **42,** 4778.
[8] *Berichte,* 1900, **33,** 171.

sodium in alcohol. It crystallises from benzene in minute colourless needles or leaflets, m.p. 160°, b.p. 161°–163°/2 mm., and is sparingly soluble in water or cold alcohol, more so in hot alcohol (1 in 10).

Ergothioneine, $C_9H_{15}O_2N_3S.2H_2O$, was found to the extent of 0·1 per cent. in ergot by Tanret.[1] It crystallises in colourless lamellæ, m.p. 290° (*decomp.*), $[\alpha]_D + 110°$, and is soluble in 8·6 parts of water at 20°, but insoluble in ether or dry alcohol. The substance is feebly basic, but forms well-defined salts, and gives precipitates with Mayer's reagent and mercuric chloride, but not with picric or tannic acids. The hydrochloride, $B.HCl.2H_2O$, m.p. 250°, (*dry*) $[\alpha]_D + 88·5°$, and the sulphate, $B_2.H_2SO_4.2H_2O$, $[\alpha]_D + 87·4°$, are crystalline, as is also the mercurichloride, $B.HgCl_2.HCl$.

Ergothioneine has been further examined by Barger and Ewins,[2] who found that it is decomposed quantitatively into trimethylamine and β-2-thiolglyoxaline-4-acrylic acid, $C_6H_6O_2N_2S$; the latter on boiling with dilute nitric acid loses sulphur and gives rise to β-glyoxalineacrylic acid. The sulphur in ergothioneine reacts in every way like that in thiolglyoxalines; thus it is oxidised by ferric chloride or bromine water to sulphuric acid with the formation of β-glyoxaline-4-propiobetaine. On these grounds Barger and Ewins have assigned the following formulæ to ergothioneine and its derivatives:

Ergothioneine   *β-2-Thiolglyoxaline-4-acrylic acid*   *β-Glyoxaline-4-acrylic acid*
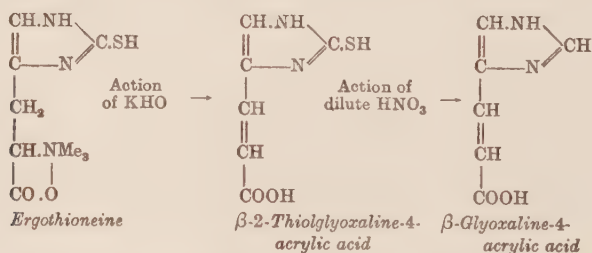
4-β-Aminoethylglyoxaline, $C_5H_9N_3$, was obtained by Barger and Dale[3] and simultaneously by Kutscher[4] from ergot extract. The substance is present in very minute amount and was isolated as the dipicrate, dark yellow rhombic plates, m.p. 234°–235° (*decomp.*), identical with the synthetic substance first prepared by Windaus and Vogt,[5] and later by Pyman.[6]

[1] *Compt. rend.* 1909, **149**, 222.
[2] *Trans. Chem. Soc.* 1911, **99**, 2336.
[3] *Ibid.* 1910, **97**, 2592.
[4] *Zeits. Physiol.* 1910, **24**, 163.
[5] *Berichte*, 1907, **40**, 3691; 1911, **44**, 1721.
[6] *Trans. Chem. Soc.* 1911, **99**, 668.

Agmatine, $C_5H_{14}N_4$, was obtained by Engeland and Kutscher [1] from ergot. It had previously been prepared by Kössel [2] from herring spawn, and was subsequently synthesised by him [3] by the action of cyanoamide in aqueous solution on tetramethylenediamine, whence it is regarded as aminobutyleneguanidine, which brings it into close relationship with arginine.

$$NH_2.C(NH).NH.CH_2.CH_2.CH_2.CH_2.NH_2$$
Agmatine

$$NH_2.C(NH).NH.CH_2.CH_2.CH_2.CH(NH_2).COOH$$
Arginine

Physiological Action of Ergot Alkaloids. Of the various bases isolated from ergot, ergotoxine, ergotamine, *p*-hydroxy-β-phenyl·ethylamine (tyramine), β-aminoethylglyoxaline (ergamine) and acetylcholine [4] are markedly active physiologically, but only the first four are of practical importance.

Ergotoxine causes all the characteristic effects of ergot,[5] viz., contraction of the uterus, rise of blood-pressure and gangrene of the cock's comb. Ergotamine, which was at first described as differing somewhat in physiological action from ergotoxine, has now been shown by Dale and Spiro to be qualitatively and quantitatively identical in its effects.[6] *p*-Hydroxyphenylethylamine causes uterine contraction and rise of blood-pressure ; β-aminoethylglyoxaline is very active : it causes contraction of the isolated uterus of the non-pregnant cat and induces a very rapid rise in blood-pressure.[7] Agmatine produces effects similar to those of the last-mentioned substance, but is far less active.[8] Ergotinine and ergothioneine are practically inert. *iso*Amylamine, also found in ergot,[9] is active, but the amount present is too small to be of physiological significance. To acetylcholine [4] are due the inhibiting action on the heart and the stimulating action on intestinal muscle shown by some samples of ergot, but this constituent is usually present in negligible amounts.

[1] *Zeits. Physiol.* 1910, **24,** 479.

[2] *Zeits. Physiol. Chem.* 1910, **66,** 257.

[3] *Ibid.* 1910, **68,** 170.

[4] Ewins, *Bio-chem. Journ.* 1914, **8,** 44, 366

[5] Dale, *Journ. Physiol.* 1906, **34,** 163 ; Barger and Dale, *Bio-chem. Journ.* 1907, **2,** 40.

[6] Dale and Spiro, *Arch. exp. Path. Pharm.* 1922, **95,** 337. *Cf. Brit. Med. Journ.* December 16, 1922, p. 1173.

[7] Dale and Laidlaw, *Journ. Physiol.* 1911, **41,** 318 ; **43,** 182.

[8] Engeland and Kutscher, *Zeits. Physiol.* 1910, **24,** 479.

[9] Barger and Dale, *Proc. Physiol. Soc.* May 15, 1909.

The scarcity of ergot, owing to failure of supplies from Russia, has led to the use of a number of substitutes including extracts of shepherd's purse (*Capsella Bursa-pastoris*). These have been asserted to contain acetylcholine, choline, and possibly tyramine,[1] as well as fumaric acid and *dl*-inositol, but, according to Wasicky,[2] plants free from fungoid infection are devoid of active constituents.

COLCHICUM AUTUMNALE

Colchicine, $C_{22}H_{25}O_6N$, is contained in the seeds and corms of the autumn crocus, *Colchicum autumnale*, in which it was first observed by Pelletier and Caventou,[3] and has since been found in numerous other species of *Colchicum* and *Merendera*,[4] and in *Gloriosa superba* (Tutin, etc.).[4] It has been investigated especially by Zeisel,[5] and more recently by Windaus.

Colchicine is prepared by treating a concentrated alcoholic extract of the seeds with water, filtering from resin and oil, and shaking out the aqueous solution with chloroform ; by repetition of this treatment, viz., solution of the residue in water and extraction with chloroform, the crystalline chloroform additive product of the base is eventually obtained in a pure state, and from this the alkaloid can be regenerated by a current of steam and crystallised from ethylacetate (Tutin) [4] or water (Merck).

The United States Pharmacopœia (9th Rev.) gives processes for the estimation of colchicine in the corms and seeds : the former are required to contain 0·35 and the seeds 0·45 per cent.[6]

Colchicine is usually seen as a yellow varnish, m.p. 143°–147° (*dry*), but it can be crystallised [7] from ethyl acetate and then forms soft pale yellow needles, m.p. 155°–157°, $[\alpha]_D^{16\cdot5} - 120\cdot6°$ in chloro-

[1] *Cf.* Boruttau and Cappenberg, *Arch. Pharm.* 1921, **259**, 33 ; van Urk, *Pharm. Weekblad,* 1921, **58**, 553 ; Grimme, *Pharm. Zentr-h.* 1921, **62**, 495 ; Zechmeister and Szécsi, *Berichte,* 1921, **54**, 172.

[2] *Ber. deut. Pharm. Ges.* 1922, **32**, 142.

[3] *Ann. Chim. Phys.* 1820 [ii], **14**, 82.

[4] *Arch. Sci. phys. nat.* 1901 [iv], **12**, 227 ; Clewer, Green and Tutin, *Trans. Chem. Soc.* 1915, **107**, 835. *Gloriosa superba* contains two other alkaloids : (1) $C_{15}H_{17}O_4N$ or $C_{33}H_{38}O_9N_2$, leaflets m.p. 177°–178° ; and (2) $C_{23}H_{27}O_6N$, needles m.p. 276°, which may be a methylcolchicine.

[5] *Monats.* 1883, **4**, 162 ; 1886, **7**, 557 ; 1888, **9**, 1, 865 ; 1913, **34**, 1181, 1327, 1339.

[6] For a discussion of processes of estimation *see* Grier, *Pharm. Journ.* July 28, 1923, p. 87.

[7] Clewer, Green and Tutin, *Trans. Chem. Soc.* 1915, **107**, 835. *Cf.* Merck, *Chem. Soc. Abstr.* 1916 [i], 833.

PLATE VII.

Colchicum autumnale. *A,* flowering plant, much reduced. *B,* lower part of the same, natural size. *C,* corm, cut vertically. *H,* fruit. *J,* the same, cut transversely, showing the seeds. *K,* seed, magnified. *L,* the same, cut to show the embryo, *e.* (Luerssen.)

form. It is miscible in all proportions with cold water, aqueous alcohol, or chloroform, less soluble in warm water (12 per cent. at 82°) or absolute alcohol. It forms a crystalline compound with chloroform, $B.2CHCl_3$, and gives an aurichloride, $B.HAuCl_4$, m.p. 209°.

The alkaloid dissolves in sulphuric acid, forming a yellow solution, which becomes green, violet, and finally red on addition of a drop of nitric acid. With ferric chloride, colchicine in hydrochloric acid solution gives a green coloration, and Fabinyi [1] has proposed this as a colorimetric method of estimation.

When treated with hydrochloric acid, colchicine furnishes methyl alcohol, acetic acid, and trimethylcolchicinic acid (I); the latter by the further action of hydrochloric acid produces three molecular proportions of methyl chloride, leaving colchicinic acid (II):

I. $C_{22}H_{25}O_6N + 2H_2O = C_{19}H_{21}O_5N + CH_3.COOH + CH_3OH.$

II. $C_{19}H_{21}O_5N + 3HCl = C_{16}H_{15}O_5N + 3CH_3Cl.$
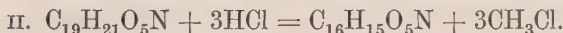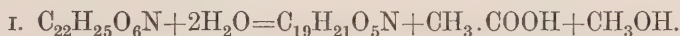
With alcoholic ammonia, methyl alcohol is split off and an amide is formed thus :

$$C_{22}H_{25}O_6N + NH_3 = CH_3OH + C_{21}H_{24}O_5N_2.$$
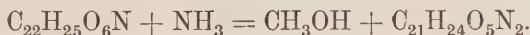
On hydrolysis by alkalis this amide yields colchiceine, $C_{21}H_{23}O_6N$ (p. 391).

The following formulæ, suggested by Zeisel, which represent colchicine as the methyl ester of colchiceine, explain these reactions :

$$C_{15}H_9 \begin{cases} (OCH_3)_3 \\ CO.O.CH_3 \\ NH.C_2H_3O \end{cases}$$
Colchicine

$$C_{15}H_9 \begin{cases} (OCH_3)_3 \\ COOH \\ NH.C_2H_3O \end{cases}$$
Colchiceine
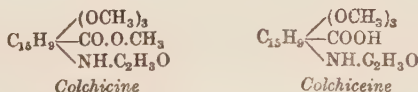
Windaus has shown [2] that on oxidation with alkaline permanganate colchicine yields 3 : 4 : 5-trimethoxy-o-phthalic acid, whilst if the product of the fusion of colchicine with potash is oxidised with permanganate trimellitic and terephthalic acids are formed, indicating the presence of a second benzene ring in the molecule.

Trimethylcolchicinic acid, which, according to Windaus, differs from colchicine as shown by the following formulæ :

[1] *Chem. Soc. Abstr.* 1912 [ii], 503. *Cf.* Davies and Grier, *Year Book of Pharmacy*, 1922, p. 436.
[2] *Sitzungsber. Heidelb. Akad. Wiss.* 1910, p. 1 ; 1911, p. 1 ; 1914, p. 18. See also footnote 1, p. 390.

$$C_{16}H_9O\left\langle\begin{array}{l}(OCH_3)_3 \\ OMe \\ NHAc\end{array}\right. \qquad C_{16}H_9O\left\langle\begin{array}{l}(OCH_3)_3 \\ OH \\ NH_2\end{array}\right.$$

Colchicine   *Trimethylcolchicinic acid*
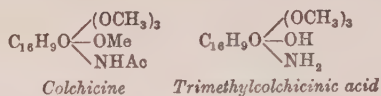
yields a dibenzoyl derivative, $(CH_3O)_3 . C_{16}H_9O(OBz) . NHBz$, which on treatment with 25 per cent. potassium hydroxide solution yields N-benzoyltrimethylcolchicinic acid ; this, unlike the dibenzoate, is coloured dark green by ferric chloride solution, and on oxidation by potassium permanganate yields N-benzoylcolchide (III). The latter when heated at 250° under reduced pressure yields benzamide and trimethoxyhomonaphthide (IV), and on further oxidation gives the 3 : 4 : 5-trimethoxy-*o*-phthalic acid referred to above.

$$C_6H(OCH_3)_3\left\langle\begin{array}{l}CH(NHBz).CH \\ \quad\quad\quad\parallel \\ CH\text{———}C \\ | \quad\quad\quad | \\ CH_2.CO.O.CH_2\end{array}\right. \qquad C_6H(OCH_3)_3\left\langle\begin{array}{l}CH\text{======}CH \\ \quad\quad\quad | \\ C\text{======}C \\ | \quad\quad\quad | \\ CH_2 . CO.O.CH_2\end{array}\right.$$

      III   IV
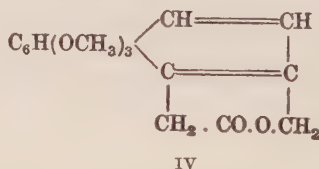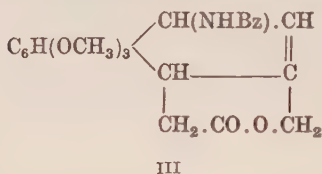
N-Benzoyltrimethylcolchicinic acid also yields on oxidation some *N*-benzoylcolchinic anhydride. This on reduction with zinc dust and acetic acid yields a tetrahydronaphthalene derivative, having the following formula :

$$C_6H(OCH_3)_3\left\langle\begin{array}{l}CH(NHBz).CH \\ \quad\quad\quad\parallel \\ CH\text{———}C \\ | \quad\quad\quad | \\ CH_2.CO.O.CO\end{array}\right. \rightarrow C_6H(OCH_3)_3\left\langle\begin{array}{l}CH (NHBz)\text{———}CH_2 \\ \quad\quad\quad\quad\quad | \\ CH_2(CH_2.COOH).CH.COOH\end{array}\right.$$

N-Benzoylcolchinic anhydride
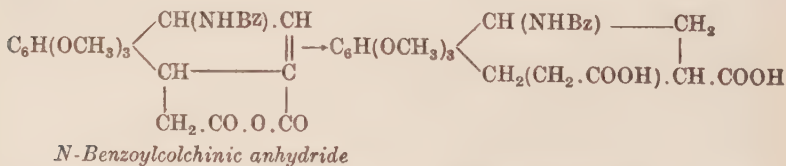
On the basis of these results, Windaus represents colchicine by the following formula, and regards it as the methyl ether of an enolic form of colchiceine :

$$CH_3O.C\underset{C.OCH_3}{\overset{CH\quad CH_2}{\underset{}{\bigcirc\bigcirc}}}C.NHCOCH_3$$

Colchicine (Windaus) [1]

[1] *Sitzungsber. Heidelb. Akad. Wiss.* 1910, p. 1,; 1911, p. 1; 1914, p. 18. In a later paper which has only recently become available in abstract form in this country, Windaus and Schiele have considerably
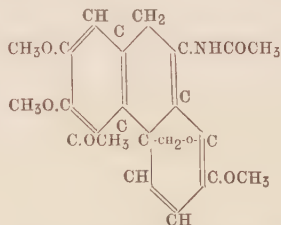
Colchiceine, $C_{21}H_{23}O_6N \cdot \frac{1}{2}H_2O$, was stated by Oberlin [1] to occur along with colchicine in the corms and seeds of the autumn crocus. According to Zeisel it is probably formed by decomposition of colchicine during extraction. Colchiceine is best prepared by heating colchicine with dilute sulphuric acid, when one molecule each of methyl alcohol and colchiceine are formed. It crystallises in colourless needles, m.p. 172° (*dry*), is readily soluble in alcohol or chloroform, and sparingly so in water, is lævorotatory and neutral in reaction. Mineral acids dissolve it, forming yellow solutions, and it is also soluble in alkaline liquids. The base gives a dark-green coloration with ferric chloride. Its relation to colchicine is shown by its mode of formation therefrom, and by the fact that it yields colchicine on methylation with sodium methoxide and methyl iodide. Windaus, therefore, represents it by the following formula :

$$C_6H(OCH_3)_3 : C_{10}H_8O(OH).NH.COCH_3$$
Colchiceine

Physiological Action. Colchicine and colchiceine appear to exert much the same physiological action, but the former has been more thoroughly investigated, and is much the more toxic of the two. It is a slow poison, no symptoms being shown for several hours after its administration, due to its slow absorption, possibly by the gradual formation of a derivative, into the central nervous system. It excites the nerve endings in plain muscle, but has no action on that in the heart or in the glands, causes marked leucocytosis and induces increased activity of the bone-marrow. Colchicine causes acute intestinal pain with nausea and diarrhœa, and in mammals poisoned with it the alimentary canal shows all the symptoms of acute gastro-enteritis, but in man the abdominal disorder is somewhat less marked. Death is due to vaso-motor paralysis. The lethal dose is about 0·0012 grm. per kilogramme of body weight.[2]

Colchicum is employed in medicine chiefly as a remedy in gout and rheumatism, and colchicine itself, mostly as the salicylate, has been used in this way.

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modified the formulæ of colchicine and some of its degradation products. *Nachr. K. Ges. Wiss Göttingen*, 1923, pp. 17–36 (*Chem. Soc. Abstr.* 1924 [i], 72).

[1] *Monats.* 1888, **9,** 870.

[2] *Cf.* Fühner, *Arch. exp. Path. Pharm.* 1913, **72,** 228.

CORYNANTHE JOHIMBE

The bark of this tree, indigenous to the Cameroons, was examined by Spiegel [1] and found to contain three alkaloids, yohimbine, meso-yohimbine, and yohimbinine. According to Siedler [2] two other alkaloids are also present.

Fourneau and Page have shown that quebrachine, which occurs in quebracho bark (p. 377), is identical with yohimbine,[3] and Fourneau and Fiore have stated that corynanthine (p. 394) found in *Pseudocinchona africana* is isomeric with yohimbine,[4] and have suggested for the latter the formula $C_{21}H_{26}O_3N_2$.

For the preparation of the alkaloids Thoms [5] extracted the bark with alcohol containing hydrochloric acid, concentrated the liquors almost to dryness, dissolved the residue in water, made the filtrate alkaline with soda and extracted with ether. The residue left on distilling off the ether was dissolved in dilute sulphuric acid and the solution shaken in succession with ether and chloroform. From this purified solution caustic soda solution precipitated the alkaloids as a white powder, which was purified by repetition of this treatment, and finally obtained in granular condition by stirring with light petroleum. It was then separated into its two components by crystallisation from hot benzene in which yohimbine is less soluble than yohimbinine. Mesoyohimbine was obtained by Spiegel by recrystallising commercial yohimbine from 50 per cent. alcohol.

Yohimbine, $C_{22}H_{28}O_3N_2 \cdot H_2O$ (Spiegel), or $C_{21}H_{26}O_3N_2$, (Fourneau and Page) crystallises from dilute alcohol in colourless needles, m.p. 234°, 247°–248° (Fourneau), $[\alpha]_D + 50 \cdot 9°$ in alcohol, is readily soluble in alcohol or chloroform, but sparingly so in ether. It forms salts with the loss of $1H_2O$; the hydrochloride[6] is crystalline, m.p. 295° 300° (*decomp.*), $[\alpha]_D^{20} + 105°$; the nitrate colourless prisms, m.p. 276°; the thiocyanate separates from hot water in rectangular

[1] *Chem. Zeit.* 1896, **20,** 970; 1897, **21,** 833; 1899, **23,** 59, 81; *Berichte*, 1903, **36,** 169; **37,** 1759; 1905, **38,** 2825; 1915, **48,** 2077, 2084; 1916, **49,** 1086.

[2] *Pharm. Zeit.* 1902, **47,** 797 (*Chem. Soc. Abstr.* 1903 [i], 195).

[3] *Bull. Sci. Pharmacol.* 1914, **21,** 7. *Cf.* Spiegel, *Berichte*, 1915, **48,** 2084; Ewins, *Trans. Chem. Soc.* 1914, **105,** 2738; Filippi, *Chem. Soc. Abstr.* 1917 [i], 582.

[4] *Bull. Soc. chim.* 1911 [iv], **9,** 1037.

[5] *Chem. Soc. Abstr.* 1898 [i], 455.

[6] *Bull. Sci. Pharmacol.* 1914, **21,** 7. *Cf.* Spiegel, *Berichte*, 1915, **48,** 2084; Ewins, *Trans. Chem. Soc.* 1914, **105,** 2738; Filippi, *Chem. Soc. Abstr.* 1917 [i], 582.

crystals, m.p. 233°–234° (Siedler). Yohimbine behaves as a tertiary base and gives a methiodide, $B.CH_3I.H_2O$, m.p. 250°. It contains one methoxyl group and yields a mono-acetyl derivative, m.p. 133°, and a sulphuric ester,[1] $B.SO_3$, m.p. 292°-295°. With bromine bromoyohimbine hydrobromide is formed, microcrystalline, m.p. 296°–298°. When heated at 120°–130° or when evaporated to dryness in dry alcohol yohimbine loses $1H_2O$ and is converted into anhydroyohimbine, $C_{22}H_{28}O_3N_2$.

When yohimbine is heated with concentrated potash solution it is converted into potassium yohimbate, $C_{20}H_{25}O_4N_2K$, from which yohimbic acid, $C_{20}H_{26}O_4N_2$ (noryohimbine), is obtained on treatment with acetic acid ; it crystallises from water in lustrous prisms, m.p. 257°–260° (*decomp.*), and on esterification with methyl alcohol and its homologues reproduces yohimbine and the homologous series of esters, whence Field concludes that yohimbine is the mono-methyl ester of the anhydrous form of yohimbic acid, $C_{20}H_{24}O_3N$, and has the empirical formula assigned to it by Fourneau and Page.[1]

Oxidation, destructive distillation with lime or soda-lime, and exhaustive methylation have all been tried with yohimbine without yielding well-defined degradation products.

It is evident from the foregoing that the chemistry of yohimbine is still in an unsatisfactory state, though it does seem to be clearly established that the alkaloid is a methyl ester, contains one hydroxyl as a secondary alcohol group, and a methoxyl group.

Mesoyohimbine, $C_{21}H_{26}O_3N_2$, crystallises in needles, m.p. 247°, is dextrorotatory, gives a crystalline hydrochloride, and contains a methoxyl group (Spiegel). It is possible that this is merely yohimbine in a purer form than that previously obtained. It is isomeric with Fourneau's yohimbine (*see above*).

Yohimbinine, $C_{35}H_{45}O_6N_3$, contained in the same plant, is a nearly colourless crystalline substance, m.p. 135°, soluble in chloroform or alcohol with a green fluorescence, but has not yet been obtained in a pure state. It is physiologically inactive.

Physiological Action. Yohimbine is poisonous ; it exerts a local anæsthetic action similar to that caused by cocaine, but is not mydriatic. The alkaloid acts as an aphrodisiac and has been so used, especially in veterinary medicine.

In recent years it has also been applied in arterio-sclerosis owing

[1] Barger and Field, *Trans. Chem. Soc.* 1915, **107**, 1025 ; 1923, **123**, 1038 ; Field, *ibid.* 1923, **123**, 3004..

to its special action on the walls of the peripheral arteries whereby the flow of blood is increased.[1]

Pseudocinchona africana

Corynanthine, $C_{21}H_{26}O_3N_2$.   From the bark of this plant Fourneau obtained this alkaloid, which is isomeric with quebrachine (p. 377) and closely resembles yohimbine (p. 392).   It crystallises from dry alcohol in hexagonal tablets or from dilute alcohol in spangles containing water of crystallisation, melts below 200° and remelts at 241°–242°, has $[\alpha]_D^{23}$ — 125° in alcohol, and yields crystalline salts.   The hydrochloride forms hexagonal leaflets, m.p. 285°–290° from alcohol, or prismatic needles, $[\alpha]_D$ — 63° with 2 to 3 H_2O from water.   The normal sulphate forms hexagonal prisms and is very soluble in water.   The methiodide occurs in prismatic needles, m.p. above 300°.   Sodium ethoxide in alcohol converts the alkaloid into an acid, $C_{20}H_{24}O_3N_2$, which Fourneau and Fiore state is isomeric with the acid similarly obtained from yohimbine.[2]   In this connection it is interesting to note that Brandt [3] has suggested in a critical review of the genera Corynanthe and Pausinystalia that Perrot's " *Pseudocinchona africana* " probably belongs to one of them.

CYTISUS LABURNUM AND OTHER PLANTS CONTAINING CYTISINE

The seeds of *Cytisus Laburnum* (*Laburnum vulgare*) and of a large number of other leguminous plants contain cytisine, which was first detected by Scott-Gray.[4]   The alkaloid was isolated in a pure state and named by Husemann and Marmé,[5] and subsequently examined by Partheil,[6] Buchka and Magelhaes,[7] van de Moer,[8] and

[1] *See especially* Müller, *Arch. intern. de pharm. et de therap.* **17,** 81.
[2] *Compt. rend.* 1909, **148,** 1770 ; 1910, **150,** 976 ; *Bull. Soc. chim.* 1911 [iv], **9,** 1037.
[3] *Arch. Pharm.* 1922, **260,** 73.
[4] *Edinb. Med. Journ.* 1862, **7,** 908, 1025.
[5] *Zeits. für. Chemie,* 1865, **1,** 161 ; **5,** 679.
[6] *Arch. Pharm.* 1892, **230,** 1 ; *Berichte,* 1890, **23,** 3202 ; 1891, **24,** 635.
[7] *Ibid.* 1891, **24,** 253, 674.
[8] *Rec. Trav. Chim.* 1891, **10,** 47.

more recently by Freund,[1] Ewins [2] and Späth.[3]   In addition to laburnum, cytisine is now known to occur in the following plants, usually in the seeds : *Ulex europæus,*[4] *Baptisia* spp., *Sophora* spp., *Genista* spp. (*cf.* p. 124, *under* Retamine), *Anagyris fœtida* (*see* p. 397), *Euchresta* spp.[5]   The amount present varies from 1·03 per cent. in *Ulex europæus* seeds to 1·87 per cent. in those of *Genista monosperma.*

Cytisine (*Ulexine, Baptitoxine, Sophorine*), $C_{11}H_{14}ON_2$.   The alkaloid is usually prepared by percolating powdered laburnum seeds with alcohol acidified with acetic acid, distilling off most of the solvent, and decanting the liquid from deposited resin and fat. The colouring matter is then removed by addition of lead acetate ; to the deleaded filtrate alkali is added in slight excess, and the liberated alkaloid shaken out with chloroform, the crude material being subsequently recrystallised from dry alcohol or purified by distillation *in vacuo.*

Cytisine forms large colourless rhombic crystals, m.p. 153°, b.p. 218° at a pressure of 2 mm., $[\alpha]_D^{17}$ — 119° 57′ in water, or — 127° 40′ at 12° (Rauwerda), is soluble in water, alcohol, or chloroform, but insoluble in ether or benzene.   Cytisine is a strongly alkaline diacidic base and forms well-crystallised salts ; the monohydrochloride, $B.HCl.H_2O$, forms colourless prisms ; the dihydrochloride, $B.2HCl.3H_2O$, yellow needles ; the aurichloride, $B.HCl.AuCl_3$, reddish-brown needles, m.p. 220°, is sparingly soluble in warm water ; the nitrate, $B.HNO_3.H_2O$, forms needles or leaflets, $[\alpha]_D$ — 81° 29′.

In aqueous solution cytisine gives a blood-red colour with ferric chloride, which is discharged by hydrogen peroxide, a blue colour being eventually developed ; nitrobenzene containing nitrothiophene produces a reddish-violet coloration.

Cytisine reacts with methyl iodide to form in turn methyl-cytisine,[6] rhombic needles, m.p. 134°, $[\alpha]_D$ — 234° 10′ in water, dimethylcytisine (amorphous) and dimethylcytisine methiodide (amorphous, deliquescent).   The last of these when heated decom-

[1] *Berichte* (with Friedmann), 1901, **34,** 605 ; 1904, **37,** 16 ; (with Horkheimer), 1906, **39,** 814 ; (with Gauff), *Arch. Pharm.* 1918, **256,** 33.

[2] *Trans. Chem. Soc.* 1913, **103,** 97.

[3] *Monats.* 1921, **40,** 15, 93.

[4] Gerrard and Symons, *Pharm. Journ.* 1889–90 [iii], **20,** 1017.

[5] *See especially* Plugge, *Rec. Trav. Chim.* 1894, **13,** 486 ; 1896, **15,** 187, with Rauwerda, *Arch. Pharm.* 1896, **234,** 685.

[6] Methylcytisine has been found by Power and Salway in *Caulo-phyllum thalictroides* (*Trans. Chem. Soc.* 1913, **103,** 194) ; it represents the alkaloid formerly called " caulophylline."

poses into trimethylamine, formaldehyde, and an amorphous base, $C_{10}H_{13}O_2N$, which yields amorphous salts (Partheil). Cytisine yields crystalline monoacetyl (m.p. 208°), monobenzoyl (m.p. 116°), and nitroso (m.p. 174°) derivatives. These reactions indicate that the alkaloid contains both a secondary and a tertiary nitrogen atom.[1]

When cytisine is oxidised with hydrogen peroxide, the imino group is converted into an $N.OH$ group, and a crystalline alkaloid, hydroxycytisine,[2] $C_{11}H_{13}ON : N.OH$, is produced. By the action of nitric acid, cytisine is converted into nitronitrosocytisine, and this on treatment with alcoholic hydrochloric acid yields nitro-cytisine, rhombic prisms, m.p. 185°–188°.

On electrolytic reduction cytisine yields tetrahydrodeoxycytisine, $C_{11}H_{20}N_2$, a strongly alkaline oil, b.p. 270°, which gives a crystalline hydrochloride, B.2HCl, m.p. 282°, $[\alpha]_D - 10° 15'$. This yields a nitroso derivative, and by treatment with methyl iodide yields first a methyl—and then a dimethyl—derivative. The latter forms a dimethiodide, $NMeI : C_{11}H_{18}.NMe_3I$, which on heating with aqueous potassium hydroxide yields trimethylamine and a viscid oil, b.p. 255°–265°.[2]

When heated with phosphorus and hydriodic acid cytisine yields ammonia and cytisoline, $C_{11}H_{11}ON$, which crystallises from alcohol in needles, m.p. 199°, is oxidised by chromic acid to cytisolinic acid $C_{11}H_9O_3N$, and is reduced by sodium in alcohol to α-cytisolidine, $C_{11}H_{15}N$, a coniine-like base, giving a platinichloride, m.p. 216°. β-Cytisolidine, which is produced along with cytisoline in the initial reduction, gives a platinichloride, m.p. 234°.[2]

It is these reduction products which have thrown most light on the constitution of cytisine. Thus Ewins[3] showed that α-cytisol-idine is 6 : 8-dimethyl-1 : 2 : 3 : 4-tetrahydroquinoline, and that β-cytisolidine, which Freund regarded as isomeric with this, has the formula, $C_{11}H_{11}N$, and is 6 : 8-dimethylquinoline. Both these products were synthesised. The same author suggested that cytisoline is probably 3 or 4-hydroxy-6 : 8-dimethylquinoline, but Späth[4] effected the synthesis of 2-hydroxy-6 : 8-dimethylquinoline, and showed that this substance was identical with cytisoline. Ewins suggested that the cytisine molecule was formed by the fusion

[1] *Cf.* Maass, *Berichte*, 1908, **41**, 1635.
[2] Freund, *Berichte* (with Friedmann), 1901, **34**, 605; 1904, **37**, 16; (with Horkheimer), 1906, **39**, 814; (with Gauff), *Arch. Pharm.*, 1918, **256**, 33.
[3] *Trans. Chem. Soc.* 1913, **103**, 97.
[4] *Monats.* 1921, **40**, 15, 93.

of three rings—benzene, pyridine and pyrazole—as shown below. Freund and Gauff [1] and Späth,[2] have proposed formulæ for cytisine based on this idea.
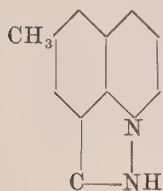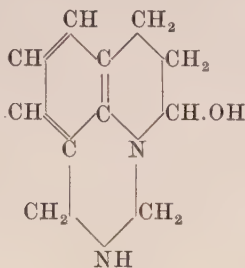
I (Ewins)   II (Freund and Gauff)   III (Späth)
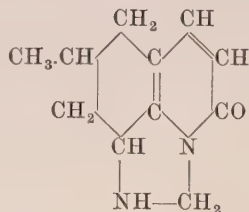
Freund and Gauff substituted a six-membered ring for the pyrazole ring on the ground that nitronitrosocytisine on oxidation with permanganate does not yield an acid, which might be expected to occur if there were a methyl group in position 6. Späth's modification is based mainly on three considerations: (1) The oxygen atom in cytisine is remarkably unreactive; (2) the alkaloid is reduced with great difficulty: hence the conjugated double linkages of the formula; (3) on oxidation with barium permanganate it yields *iso*valeric acid.

Physiological Action. Cytisine is a powerful poison causing nausea, convulsions, and death by asphyxiation. In small doses the hydrobromide has been suggested as a diuretic. According to Dale and Laidlaw,[3] it closely resembles nicotine in physiological action.

Anagyris fœtida

Anagyrine, $C_{15}H_{22}ON_2$, obtained with cytisine (p. 395) from the seeds of *Anagyris fœtida* by Partheil and Spasski,[4] and subsequently investigated by Klostermann [5] and by Litterscheid,[6] is an amorphous varnish-like substance. The hydrochloride, $B.HCl.H_2O$, crystallises

[1] Freund, *Berichte* (with Friedmann), 1901, **34**, 605; 1904, **37**, 16; (with Horkheimer), 1906, **39**, 814; (with Gauff), *Arch. Pharm.*, 1918, **256**, 33.
[2] *Monats.* 1921, **40**, 15, 93.
[3] *Journ. Pharm. exp. Ther.* 1912, **3**, 205.
[4] *Apoth. Zeit.* 1895, **10**, 903.
[5] *Arch. Pharm.* 1900, **238**, 227.
[6] *Ibid.* 1900, **238**, 191.

in rhombic plates, $[\alpha]_D - 142° 28'$; the hydriodide, $B.HI.H_2O$, forms stellar aggregates of yellow needles, the platinichloride, $B.2HCl.PtCl_4.1\frac{1}{2}H_2O$, ruby-red needles, m.p. above 235°; and the methiodide, $B.CH_3I$, colourless needles.

When oxidised with permanganate a crystalline product, $C_{15}H_{20}O_2N_2$, m.p. 195°, is formed. Anagyrine contains no hydroxyl group, is ditertiary, and has the composition and properties of a butylcytisine, but Goessmann[1] has thrown doubt on the validity of the formula, $C_{15}H_{22}ON_2$, usually assigned to the base.

In cold-blooded animals anagyrine exerts a curare-like action, and in warm-blooded species induces depression of respiration. Its physiological action is unlike that of cytisine.

Sophora Angustifolia (S. Flavescens)

Cytisine is the typical alkaloid of the genus Sophora, but from this species a distinct alkaloid matrine has been isolated by Nagai and by Plugge,[2] and recently further investigated by Kondo and collaborators.[3]

Matrine, $C_{15}H_{24}ON_2$, melts at about 80°, is dextrorotatory in solution, and yields a platinichloride, aurichloride, and a crystalline ferrocyanide. It is a monoacidic, ditertiary base. One of the nitrogen atoms forms a lactam ring with a carboxyl group, and is converted into an imino group by the action of alkali yielding matrinic acid. On distillation with zinc dust, matrine yields a mixture of two bases, $C_{10}H_9N$, b.p. 188°–189°/760 mm., and a second, $C_{15}H_{26}N_2$, called MATRIDINE, colourless needles, m.p. 76°. On reduction with sodium and amyl alcohol, matrine yields DEOXY-MATRINE, $(C_{15}H_{24}N_2)_2$, rhombic prisms, m.p. 162°, and this on further reduction with hydriodic acid gives DIMATRIDINE, $(C_{15}H_{25}N_2)_2$, long colourless needles, m.p. 160°. From these and other results partial formulæ for matrine and some of its degradation products have been developed.

DAPHNANDRA SPP.

In 1886, T. L. Bancroft[4] showed that alkaloids were present in several members of this genus, especially *D. repandula* and *D.*

[1] *Arch. Pharm.* 1906, **244,** 20.

[2] *Ibid.* 1895, **233,** 441.

[3] *J. Pharm. Soc. Japan*, 1889, No. 84; 1903, Nos. 260–262; 1921, p.659, 1047; 1923, No. 498, p. 644 (*Chem. Soc. Abstr.* 1921 [i], 882; 1922 [i], 269; 1924 [i], 76).

[4] *Proc. Roy. Soc. N.S.W.* 1886, **20,** 70.

micrantha.   The latter species was examined by Pyman [1] and shown to contain three alkaloids, daphnandrine, micranthine and daphnoline.

Daphnandrine, $C_{36}H_{38}O_6N_2$, crystallises from chloroform (with solvent of crystallisation) in colourless needles, m.p. 280° (dried at 100°, *decomp.*), $[\alpha]_D + 474 \cdot 7°$ (dry base, in chloroform).   The hydrochloride, $B.2HCl.5H_2O$, forms colourless prisms, m.p. 282° (*dried, decomp.*), $[\alpha]_D + 296$ to 314° (in water $c = 3 \cdot 9$ to $1 \cdot 1$), from water ; the hydrobromide, $B.2HBr.6H_2O$, colourless prisms, m.p. 291° (*dry, decomp.*) from water ; and the acid oxalate, $B.1\frac{1}{2}H_2C_2O_4$. $5\frac{1}{2}H_2O$, colourless needles, m.p. 225° from alcohol.   The alkaloid is characterised by sparing solubility in nearly all solvents, except boiling chloroform.   It contains three methoxyl groups and one methylimino group.

Micranthine, $C_{36}H_{32}O_6N_2$, crystallises from chloroform in colourless needles (with solvent of crystallisation), m.p. 190°–196°, insoluble in water or ether, sparingly in alcohol or chloroform, yields a crystalline sulphate, $B.H_2SO_4.10H_2O$, fine colourless needles, m.p. 312° (*decomp.*), from boiling water.   No other crystalline salt was obtained.   The base contains one .OMe and one : NMe group.

Daphnoline, $C_{34}H_{34}O_6N_2$, crystallises from alcohol or chloroform in small hexahedra (with solvent of crystallisation), m.p. 190°–215°, $[\alpha]_D + 459°$ (dry base in chloroform), and is even less soluble than daphandrine in all ordinary solvents.   The hydrochloride, $B.2HCl$. $3\frac{1}{2}H_2O$, forms, from alcohol, large colourless double pyramids, m.p. 290° (*dry, decomp.*), $[\alpha]_D + 283°$ (hydrated salt in water), and the hydrobromide, $B.2HBr.4H_2O$, microscopic needles, m.p. 286° (*decomp.*) from hot water.   Daphnoline is a phenolic base, contains two methoxyl groups and one methylimino group.

The three alkaloids give characteristic colour reactions with Fröhde's reagent : daphnandrine, indigo-blue changing to port wine red ; micranthine, indigo-blue changing to emerald-green ; daphnoline, violet changing to port-wine red.

According to Dale [2] all three alkaloids exhibit the same type of pharmacological action, but daphnandrine is only slightly active. Daphnoline and micranthine produce on hypodermic injection marked local action causing œdematous infiltration of the subcutaneous tissues and loss of sensibility.   They also have a depressant action on the central nervous system, and, when given intra-

[1] *Trans. Chem. Soc.* 1914, **105,** 1679.
[2] Quoted by Pyman, *loc. cit. p.* 1680.

venously, cause vasodilator circulatory depression. Death from large doses is due to respiratory paralysis.

DELPHINIUM SPP.

From *Delphinium bicolor, D. Menziesii, D. scopulorum,* and *D. Nelsonii* roots, Heyl isolated quantities varying from 0·27 to 1·30 per cent. of a mixture of alkaloids which he called " delphocurarine " since it exerted a strong curare-like action on peripheral nerve endings.[1] The chief constituent is an alkaloid, $C_{23}H_{33}O_7N$, which crystallises in needles, m.p. 184°–185°, dissolves in alcohol or chloroform, but not in light petroleum, and yields methyl iodide corresponding to $OCH_3 = 18·03$ per cent., when heated with hydriodic acid. The salts are amorphous and the alkaloid gives no colour reaction with sulphuric or nitric acid. According to Lohmann, delphocurarine can be employed in place of curarine in physiological investigations.[2]

Uncharacterised alkaloids are also recorded for *D. glaucum* and *D. geyeri.*[3]

Delphinium Ajacis

From the seeds of this species, Keller and Völker [4] isolated two alkaloids.

Ajacine, $C_{15}H_{21}O_4N.H_2O$, separates in colourless needles, m.p. 142°–143° from dilute alcohol, is alkaline in reaction, and yields readily soluble salts which crystallise with difficulty. The alkaloid contains three methoxyl groups.

Ajaconine, $C_{17}H_{29}O_2N$, crystallises in glancing prisms, m.p. 162°–163°, yields a methiodide, slender needles, m.p. 121°, appears to be a secondary base, yields an amorphous dibenzoyl derivative, and contains no methoxyl groups.

Delphinium Consolida

From the seeds of this species Keller [5] isolated three alkaloids, of which the most important crystallises in hexagonal prisms, m.p. 195°–197°, is strongly alkaline in solution and highly toxic.

[1] *Chem. Soc. Abstr.* 1903 [i], 650.
[2] *Pfluger's Archiv.* 1902, **92**, 398.
[3] Heyl, Hepner and Loy, *Journ. Amer. Chem. Soc.* 1913, **35**, 880.
[4] *Arch. Pharm.* 1913, **251**, 207.
[5] *Ibid.* 1910, **248**, 468.

Delphinium Staphisagria

Delphinine, $C_{31}H_{49}O_7N$ or $C_{34}H_{47}O_9N$, was obtained in 1819 by Brandes from the seeds of *Delphinium Staphisagria*, and has since been examined by Kara-Stojanow,[1] who assigned to it the formula, $C_{31}H_{49}O_7N$, recently altered by Walz [1] to $C_{34}H_{47}O_9N$.

It crystallises in rhombs, begins to decompose at 120° and melts at 191·8°; it is soluble in the usual organic solvents, but not in water. The acid oxalate crystallises in needles. Delphinine is a tertiary base, contains a benzoyl group, four methoxyl groups and one free hydroxyl group (Walz [1]). According to Keller,[2] commercial delphinine is a mixture of two crystalline alkaloids. It is intensely poisonous, resembling aconitine in its action and affecting especially the respiration and circulation by paralysing the nerves of the respiratory system. The lethal dose for dogs is 0·0015 grm. per kilogramme of body weight.

Delphisine. This isomeride of delphinine closely resembles it in physical properties. It melts at 189°. The lethal dose for dogs is 0·0007 grm. per kilogramme of body weight.

Delphinoidine, $C_{25}H_{42}O_4N$ (?), is an amorphous base slightly soluble in water and organic solvents, and differing from the two foregoing alkaloids in giving a yellow colour changing to red and then blue when mixed with malic acid and moistened with sulphuric acid. The lethal dose for dogs is 0·0005 grm. per kilogramme of body weight.

Staphisagroine, $C_{40}H_{46}O_7N_2$,[3] is an amorphous alkaloid, m.p. 275°–277°. It is insoluble in all ordinary solvents and remains as a yellow powder when the crude mixed alkaloids obtained as described above are dissolved in a little chloroform.

GALIPEA CUSPARIA

The bark of *Galipea Cusparia* (*Cusparia febrifuga*) has long been used as a febrifuge in the West Indies, and its popular name "angostura," will doubtless recall other forms in which it is imported into this country. The presence of an alkaloid in the bark was first noted by Oberlin and Schlagdenhauffen, and Körner and Böhringer isolated cusparine and galipine from it in 1883.[4] Beckurts has also

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[1] *Chem. Cent.* 1890 [ii], 628. *Cf.* Walz, *Arch. Pharm.* 1922, **260,** 9.
[2] *Arch. Pharm.* 1910, **248,** 648.
[3] Ahrens, *Berichte,* 1899, **32,** 1581, 1669.
[4] *Berichte,* 1883, **16,** 2305.

investigated this bark, and, in addition to further characterising cusparine and galipine, has obtained the new bases "galipidine," "cusparidine,"[1] and "cuspareine,"[2] whilst Tröger and his colleagues have extended our knowledge of cusparine and galipine, have added galipoidine and an unnamed alkaloid ($C_{16}H_{13}O_2N$, m.p. 186°, yellow rhombic crystals) to the list,[3] and have shown that of Beckurts' three new bases "galipidine" and "cusparidine" are probably mixtures of the first two, and have not been able to find cuspareine. The well-defined alkaloids of the bark are, therefore, three, *cusparine, galipine* and *galipoidine*. A method for the isolation and separation of the alkaloids is given by Tröger and Müller.[3]

Cusparine, $C_{19}H_{17}O_3N$, exists in three forms, colourless needles, m.p. 90°–91°, long yellow needles, m.p. 91°–92°, and amber-tinted crystals, m.p. 110°–122°.[4] It is readily soluble in alcohol or ether. The salts are sparingly soluble in water and are readily separated from the salts of the associated alkaloids ; the hydrochloride, $B.HCl.3H_2O$, forms needles, the oxalate, $B.H_2C_2O_4.1\frac{1}{2}H_2O$, m.p. 140°–150°, sulphur-yellow needles from water ; the platinichloride, $B_2.H_2PtCl_6.3H_2O$, m.p. 210°, glancing yellow needles ; the aurichloride, $B.HCl.AuCl_3$, has m.p. 190°. The salts with organic acids on melting yield PYROCUSPARINE, $C_{18}H_{15}O_3N$, needles, m.p. 255° from alcohol.[5] Cusparine contains one methoxyl, but no hydroxyl group. It reacts with methyl iodide as a tertiary base, and the methiodide, yellow prisms, m.p. 190°, gives, on treatment with silver oxide, not methylcusparine, $C_{20}H_{18}O_3N.CH_3$, as previously supposed, but *iso*cusparine, m.p. 194°, in which the methyl of the methoxyl group in cusparine is believed to have migrated to the N-atom.[6] With dilute nitric acid cusparine gives "nitrocusparine," $C_{17}H_{14}O_4N_2.H_2O$, m.p. 143°, which, like the parent base, contains one methoxyl group. When heated for several days with nitric acid (sp. gr. = 1·075) at 100°, cusparine yields an acid, $C_{10}H_7O_3N.H_2O$, m.p. 271°–272°, which is probably a hydroxyquinolinecarboxylic acid.[7] On fusion with potassium hydroxide, the alkaloid yields protocatechuic acid.

[1] *Arch. Pharm.* 1891, **229,** 591 ; 1895, **233,** 410 ; 1905, **243,** 470.
[2] *Apoth. Zeit.* 1903, **18,** 697.
[3] *Arch. Pharm.* 1910, **248,** 1 ; 1911, **249,** 174.
[4] For description of crystalline form, *see* Maria de Angelis, *Atti. R. Accad. dei. Lincei,* 1921 [v], **30,** 328.
[5] Tröger and Beck, *Arch. Pharm.* 1913, **251,** 246.
[6] Tröger and Müller, *ibid.* 1914, **252,** 459.
[7] Tröger and Beck, *ibid.,* 1913, **251,** 246.

Cusparine gives a cherry-red coloration with sulphuric acid and a deep blue with Fröhde's reagent.

Galipine, $C_{20}H_{21}O_3N$, crystallises from alcohol or ether in prisms, m.p. 115·5°, and yields crystalline salts, which are more soluble than those of cusparine. The hydrochloride, $B.HCl.4H_2O$, forms leaflets; the aurichloride, $B.HAuCl_4$, and the platinichloride both melt at 174°–175°. The methiodide, BCH_3I, forms yellow needles, m.p. 146°. Galipine contains three methoxyl groups. On oxidation with chromic acid it yields veratric and anisic acids and a third acid, $C_{11}H_9O_3N.2H_2O$, m.p. 194°, which is probably a methoxyquinoline carboxylic acid. On destructive distillation with zinc dust, galipine yields quinoline. The following formula has been suggested for the alkaloid; [1] the position of the methoxyl group in the quinoline nucleus is uncertain.
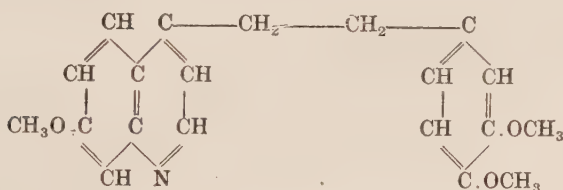
Galipine

Galipoidine, $C_{19}H_{15}O_4N$, m.p. 233°, is sparingly soluble in most organic solvents; it forms a platinichloride, $B_2.H_2PtCl_6.2\frac{1}{2}H_2O$, crystallising in stout yellow prisms and decomposing at 158°, and an abnormal aurichloride, $(B.HCl)_2.AuCl_3.1\frac{1}{2}H_2O$, m.p. 170° (*decomp.*), crystallising in bright yellow needles.

Physiological Action.—These alkaloids have not been investigated physiologically. Cusparia bark, as already indicated, is employed as a febrifuge and a bitter tonic, but probably its most important use is in the preparation of liqueurs.

GELSEMIUM SEMPERVIRENS

The rhizome and roots of this North American plant, known as "yellow jasmine" in the United States, have long been used in medicine and are still recognised in several pharmacopœias.

The existence of alkaloidal constituents in the drug was first demonstrated by Wormley; [2] some years later a crystalline alkaloid

[1] Tröger and Kroseberg, *Arch. Pharm.* 1912, **250**, 494.
[2] *Amer. J. Pharm.* 1870, **42**, 1.

was isolated by Gerrard [1] and named gelsemine. The root was reinvestigated by Thompson [2] and shown to contain in addition to gelsemine an amorphous alkaloid, gelseminine. Gelsemine has been examined more recently by Spiegel [3] and by Göldner,[4] who agreed in assigning to it the formula $C_{22}H_{26}O_3N_2$. The drug has been reinvestigated by Moore,[5] who obtained gelsemine in a pure state and assigned to it the new formula, $C_{20}H_{22}O_2N_2$. According to Moore, two other alkaloids, both amorphous, one of which corresponds to Thompson's " gelseminine " are also present.

Gelsemine, $C_{20}H_{22}O_2N_2$, crystallises from acetone with one molecule of the solvent in glistening prisms, m.p. 178°, which lose their acetone at 120°, has $[\alpha]_D + 15\cdot9°$ in chloroform, is readily soluble in alcohol, chloroform, or ether, and slightly so in water. The hydrochloride, B.HCl, crystallises from dilute alcohol or water in prisms, m.p. 300°, $[\alpha]_D + 2\cdot6°$ in water ; and the nitrate, B.HNO_3, from water in glistening prisms, m.p. above 280°.

Gelsemine contains one hydroxyl group, and with acetic anhydride yields acetylgelsemine, $C_{20}H_{21}ON_2.OAc$, which crystallises from methyl alcohol with one molecule of the solvent in colourless prisms, m.p. 60°–70° or 106°–108° (*dry*). Gelsemine methiodide, B.$CH_3I.H_2O$, separates from alcohol in large prisms or from water in glancing leaflets ; with potassium hydroxide solution it regenerates gelsemine. When boiled with hydrochloric acid, gelsemine takes up one molecule of water, forming apogelsemine, $C_{20}H_{24}O_3N_2$, an amorphous base which yields crystalline salts, together with *iso*apogelsemine (m.p. 310°) and chloro*iso*apogelsemine, $C_{20}H_{23}O_2N_2Cl$. The first two of these products yield diacetyl derivatives.

Gelsemine dissolves in strong sulphuric acid, giving a colourless solution, which on the addition of a crystal of potassium dichromate becomes red, then violet, and finally green.

Amorphous Alkaloids. From the alkaline liquid after removal of gelsemine by ether, Moore [5] observed that amyl alcohol removed a product consisting of two amorphous alkaloids, of which the more basic probably corresponds with Thompson's gelseminine, but no crystalline derivatives of either could be obtained.

[1] *Pharm. Journ.* 1883 [iii], **13**, 641.
[2] *Ibid.* 1887 [iii], **17**, 803.
[3] *Berichte*, 1893, **26**, 1045.
[4] *Ber. deut. pharm. Ges.* 1895, **5**, 330.
[5] *Trans. Chem. Soc.* 1910, **97**, 2223 ; 1911, **99**, 1231. *Cf.* Sayre, *Journ. Amer. Pharm. Assoc.* 1919, **8**, 708.

Physiological Action. Cushny has shown [1] that gelsemine hydrochloride is inactive to mammals, but produces strychnine-like effects in frogs, and Dale, working with Moore's material,[2] found that in doses of 0·1 grm. it produced no effect on rabbits. On the other hand, 0·001 grm. of the hydrochlorides of the mixed amorphous alkaloids injected into rabbits caused convulsions followed by death from respiratory failure. According to Cushny, the amorphous " gelseminine " resembles coniine in physiological action, but possesses a greater depressant action on the central nervous system and, unlike coniine, causes no rise in blood-pressure. It is also a powerful mydriatic when applied locally, but less so when taken internally.

GEISSOSPERMUM VELLOSII

The bark of this plant, known as " pereiro bark," is used in Brazil as a febrifuge. Hesse isolated from it the two alkaloids, geissospermine and pereirine,[3] and a third, vellosine, was found by Freund and Favet.[4]

Geissospermine, $C_{19}H_{24}O_2N_2 . H_2O$, crystallises from hot alcohol in small prisms, m.p. 160°, $[\alpha]_D - 93·37°$ in alcohol, becomes anhydrous at 100°, and is sparingly soluble in water, ether, or cold alcohol. The sulphate, $B_2 . H_2SO_4$, is crystalline, and the platinichloride forms bright yellow needles. The alkaloid gives a colourless solution with sulphuric acid, which slowly turns blue on standing.

Pereirine, $C_{19}H_{24}ON_2$ (?), is amorphous ; it gives a violet-red coloration with sulphuric acid.

Vellosine, $C_{23}H_{28}O_4N_2$, crystallises from hot alcohol in four-sided prisms, m.p. 189°, $[\alpha]_D + 22·8°$ in chloroform, is readily soluble in warm alcohol or benzene, or in cold chloroform or ether. It yields crystalline salts ; the hydrobromide, m.p. 194°–195°, and the hydriodide, m.p. 217°–218°, both crystallise with one molecule of water. Vellosine contains two methoxyl groups and behaves as a monoacidic tertiary base. On heating with mineral acids it loses water, forming apovellosine, $C_{46}H_{54}O_7N_4$.

In physiological action it resembles brucine and is toxic to rabbits in doses of 0·075 grm. per kilogramme of body weight.[4]

[1] *Berichte,* 1893, **26,** 1045 ; *Arch. exp. Path. Pharm.* **31, 49.**
[2] *Berichte,* 1893, **26,** 1045.
[3] *Annalen,* 1880, **202, 141.**
[4] *Ibid.* 1894, **282, 247.** *Cf.* Hesse, p. 266.

HOLARRHENA SPP.

In 1858, Haines [1] isolated from the bark of *Holarrhena* (*Wrightia*) *antidysenterica*, known as " Kurchi " in India, the alkaloid now known as conessine. It was prepared from the seeds of the same plant independently by Stenhouse [2] in 1864, and by him called wrightine. In 1886, Polstorff and Schirmer [3] found the same alkaloid in *H. africana*, and in 1919, Pyman [4] isolated it from a second African species, *H. Congolensis*, together with a new alkaloid, holarrhenine ; it has also been recorded in *H. Wulfsbergii*. Conessine has been investigated by Ulrici,[5] and by Giemsa and Halberkann.[6]

Conessine, $C_{24}H_{40}N_2$, crystallises from boiling acetone in large colourless plates, m.p. 125°, $[\alpha]_D - 1.9°$ (in chloroform),[4] $+ 21.6°$ (in dry alcohol).[5] The hydrochloride, $B.2HCl.H_2O$, forms masses of minute silky needles, m.p. above 340°, $[\alpha]_D^{20} + 9.3°$ (in water) ; [6] the hydrobromide [4] has $[\alpha]_D + 7.4°$, the acid oxalate, $B.2H_2C_2O_4$, crystallises in prisms, m.p. 280° (*decomp.*), readily soluble in hot and sparingly in cold water. The platinichloride, $B.H_2PtCl_6$, is a crystalline powder.[6] The alkaloid forms a dimethiodide, $B.(MeI)_2.3H_2O$, m.p. above 285°, and the quaternary ammonium base obtained from this yields trimethylamine on distillation. On oxidation with potassium iodate in presence of dilute sulphuric acid DIOXYCONESSINE, $C_{24}H_{42}O_2N_2$, is formed. This crystallises from alcohol on addition of water in small thick needles, m.p. 294°–295°, $[\alpha]_D + 11.79°$ (in alcohol), and gives a crystalline platinichloride, $B.H_2PtCl_6.3H_2O$, ruby or orange needles, which effloresce *in vacuo* or when warmed, forming an orange-yellow powder. Dioxyconessine forms an amorphous dibenzoyl derivative, which is still diacidic, so that the two oxygen atoms appear to be present as hydroxyl groups. On further oxidation with chromic acid, it yields dimethylamine and a lactone acid, $C_{22}H_{33}O_4N$, which has probably not been obtained pure.

Holarrhenine, $C_{24}H_{38}ON_2$, crystallises from ethyl acetate in silky needles, m.p. 197°–198°, $[\alpha]_D - 7.1°$ (in chloroform), is soluble in alcohol or chloroform, but sparingly so in cold ethyl acetate, acetone

[1] *Pharm. Journ.* 1865 [ii], **6,** 432.
[2] *Ibid.* 1864 [ii], **5,** 493.
[3] *Berichte,* 1886, **19,** 78. *Cf.* Warnecke, *Inaug. Diss. Erlangen,* 1888.
[4] *Trans. Chem. Soc.* 1919, **115,** 163.
[5] *Arch. Pharm.* 1918, **256,** 57.
[6] *Ibid.* p. 201.

or ether. The hydrobromide, $B.2HBr.3H_2O$, crystallises from water in flat needles, m.p. 265°–268° (*dry*), $[\alpha]_D + 11.0°$ in water. The alkaloid contains, like conessine,[1] three N-alkyl (probably methyl) groups (Herzig-Meyer method), and the oxygen is present as hydroxyl, since the alkaloid yields an acetyl derivative, oblong plates (m.p. 180°, from acetone), which is still diacidic.[1]

Physiological Action. According to Keidel,[2] conessine resembles morphine in action and is toxic, producing narcosis and finally death from paralysis of the respiratory centre. Giemsa and Halberkann, on the contrary, were able to give comparatively large doses by the mouth to dogs and to human beings without producing narcosis, and Burn [3] finds that though both conessine and holarrhenine induce narcosis in frogs, this effect is inappreciable in mammals. Both alkaloids produce local anæsthesia, but are of no value for this purpose, since they cause local necrosis on subcutaneous injection.

Oxyconessine has no general or local anæsthetic action, but produces a curare-like effect in frogs. "Kurchi" bark is chiefly used in India as a remedy for dysentery, and although conessine is no doubt, responsible for the value of the bark in this disease, it has so far not been possible to make use of the alkaloid itself or one of its derivatives for this purpose.[4]

LAURELIA NOVÆ-ZELANDIÆ

From the bark of this tree, known as the "Pukatea" in New Zealand, Aston [5] isolated the following three alkaloids:

Pukateine, $C_{17}H_{17}O_3N$, crystallises from alcohol, has m.p. 200°, $[\alpha]_D^{15} - 220°$ in alcohol, and is feebly basic, being extracted from acetic acid solution by chloroform. It is sparingly soluble in light petroleum, more so in chloroform or ether (0.62 in 100 at 17°), and very soluble in pyridine. It also dissolves in solutions of alkali hydroxides, forming metallic derivatives, from which the alkaloid is regenerated by carbon dioxide. The hydrochloride, $B.HCl$, is crystalline. No methoxyl groups are present. Sulphuric acid gives a dull purple coloration with pukateine on warming. Nitric acid gives a dark red coloration. On exposing the alkaloid in sodium hydroxide

[1] *Trans. Chem. Soc.* 1919, **115**, 163.
[2] *Inaug. Diss. Göttingen*, 1878.
[3] *Journ. pharm. Exp. Ther.* 1915, **6**, 305 (quoted by Pyman).
[4] *See for example*, Brown, *Brit. Med. Journ.* 1922 [i], 993; Henry and Brown, *Trans. Roy. Soc. Trop. Med. and Hyg.* 1923, **17**, 61, 381; Willmore, *ibid.* p. 22.
[5] *Trans. Chem. Soc.* 1910, **97**, 1381.

solution to the air for a few hours it becomes green, and on acidifying with hydrochloric acid and shaking with ether the latter develops a purple tint.

According to Malcolm, pukateine hydrochloride in doses of 0·25 grm. per kilogramme of body weight has a convulsant action on the nerve-cells of the spinal cord. In rabbits the convulsions resemble those induced by strychnine. On intravenous injection the blood-pressure falls slightly, the heart beats slowly, and death results from respiratory failure. Applied to the tongue, pukateine causes numbness. The alkaloid itself is inactive, owing to its insolubility.

Laureline, $C_{19}H_{21}O_3N$, has been obtained only in the form of its salts. The sulphate, $B_2.H_2SO_4.7H_2O$, m.p. 105°, crystallises from dilute sulphuric acid ; the hydrochloride, B.HCl, is also crystalline.

Laurepukine, $C_{16}H_{19}O_3N$, is yellowish white and amorphous.

LOBELIA INFLATA

The presence of alkaloids in this plant was first demonstrated by Procter.[1] Later on Lewis [2] obtained the chief alkaloid lobeline in the form of a strongly basic viscous oil, and this was examined by Siebert,[3] who prepared and analysed several crystalline salts and assigned to the alkaloid the formula, $C_{18}H_{23}O_2N$. Quite recently, interest in the plant has revived, processes for the isolation and purification of its alkaloids have been patented,[4] and at present the subject is in a somewhat confused state. According to one series of patents, the plant contains three alkaloids : α-lobeline, $C_{21}H_{23}O_2N$, colourless crystals, m.p. 120° ; β-lobeline, amorphous, but yielding a crystalline hydrochloride, sparingly soluble in water ; and γ-lobeline, amorphous and yielding amorphous salts. Wieland,[5] on the contrary, has isolated two crystalline alkaloids from the plant.

Lobeline, $C_{23}H_{29}O_2N$. This is described as forming broad colourless needles, m.p. 130°–131°, $[\alpha]_D^{15} - 42.85°$ (in alcohol), neutral in reaction, and yielding crystalline salts, of which the hydrochloride, m.p. 182°, is unusual in being removable from aqueous solution by chloroform. The alkaloid is monoacidic, does not contain carbonyl,

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[1] *Amer. Journ. Pharm.* 1836, **9,** 98. *Cf.* Bastick, *Pharm. Journ.* 1850 [i], **10,** 270, 456.

[2] *Pharm. Journ.* 1877–78 [iii], **8,** 56.

[3] *Inaug. Diss. Marburg.* 1891.

[4] British Patent 145,621 (*Chem. Soc. Abstr.* 1921 [i], 267) ; German Patents 336,335, 340,116.

[5] *Berichte,* 1921, **54,** 1784.

hydroxyl or methoxyl groups, but has the remarkable property of yielding acetophenone when warmed with water.

Lobelidine, $C_{20}H_{25}O_2N$, forms small irregular prisms, m.p. 106°, and yields a hydrochloride, m.p. 165°.

Physiological Action. According to Edmunds [1] lobeline causes first excitation, then depression of the central nervous system with loss of reflexes, and a curare-like action on the muscles. In cats and dogs it is a powerful emetic, and in large doses produces muscular twitchings, then convulsions, and finally death. In small doses it stimulates, and in large doses paralyses the respiratory centre. On cold-blooded hearts it acts almost like nicotine, and is also stated to inhibit the action of muscarine. *Lobelia inflata* leaves were formerly used in medicine as an emetic, but now they are only employed as a remedy for spasmodic asthma.

LUPINUS SPP.

The seeds of the various species of Lupinus have been the subject of several investigations, in the course of which four alkaloids have been isolated : [2] lupinine, $C_{10}H_{19}ON$, and sparteine (lupinidine),[3] from *L. luteus* and *L. niger* (*see* p. 120) ; lupanine, $C_{15}H_{24}ON_2$, from *L. angustifolius*, *L. perennis*, and *L. albus* ; and hydroxylupanine, $C_{15}H_{24}O_2N_2$, from *L. perennis*.

Lupinine, $C_{10}H_{19}ON$. The alkaloidal constituents of yellow lupin seeds were first isolated by Cassola [4] in 1835, but lupinine itself was first obtained pure by Baumert [5] and later by Schmidt and Berend.[6] The alkaloid is best prepared by percolating the ground seeds with alcohol containing 1 per cent. of hydrochloric acid. From this extract the solvent is distilled off, and the residue, after neutralisation with soda and extraction with ether to remove fat, treated with mercuric chloride to precipitate sparteine as the mercurichloride. The filtrate is then deleaded, made alkaline with soda, and the liberated lupinine extracted with ether. According to

[1] *Amer. Journ. Physiol.* 1904, **11**, 79. *Cf.* Eckstein, Rominger and Wieland, *Zeit. für Kinderheilkunde*, 1921, **28**, 218.

[2] Schmidt and others, *Arch. Pharm.* 1897, **235**, 192 ; (Davis) 199, 218, 229 ; (Berend) 262 ; (Gerhard) 342, 355 ; (Callsen) 1899, **237**, 566 ; (Bergh) 1904, **242**, 416 ; (Beckel) 1912, **250**, 691.

[3] Lupinidine was shown to be identical with sparteine by Willstätter and Marx, *Berichte*, 1904, **37**, 2351.

[4] *Annalen*, 1835, **13**, 308.

[5] *Berichte*, 1881, **14**, 1150, 1321, 1880, 1882 ; 1882, **15**, 631, 1951.

[6] *Arch. Pharm.* 1897, **235**, 263.

Willstätter and Fourneau, lupinine is readily extracted from a mixture of lupinine and sparteine by light petroleum.[1]

The alkaloid separates from light petroleum in rhombic crystals, m.p. 68·5°-69·2°, b.p. 255°-257°, in a current of hydrogen, $[\alpha]_D^{17} - 19°$; it is a strong base and liberates ammonia from its salts.   The hydrochloride, B.HCl, forms rhombic prisms, m.p. 212°–213°, $[\alpha]_D - 14°$ in water, and the aurichloride, B.HAuCl$_4$, agglomerations of needles, m.p. 196°–197°.

With benzoic anhydride lupinine forms benzoyllupinine, minute needles, m.p. 49°–50°, and when heated with phosphoric anhydride, loses one molecule of water, forming anhydrolupinine, $C_{10}H_{17}N$, a colourless oil, b.p. 216°–217°/726 mm.

On oxidation by chromic acid, the alkaloid forms lupininic acid, $C_9H_{16}N.CO_2H$, long needles, m.p. 255°, by the conversion of a primary alcohol group into carboxyl.   The nitrogen in lupinine has no methyl group attached to it, but reacts as a tertiary nitrogen, giving a methiodide, from which methyllupinine can be prepared by the action of silver oxide.   By repeating this process, lupininedimethylammonium hydroxide is obtained, and this when distilled breaks up into trimethylamine and an unsaturated alcohol, $C_{10}H_{15}OH$.   These observations have led Willstätter and Fourneau [1] to suggest that lupinine contains a bicyclic nucleus with a nitrogen atom common to both rings similar to that of quinuclidine.

Lupanine, $C_{15}H_{24}ON_2$.[2]   This alkaloid occurs in the dextro- and inactive modifications in the white lupin, and in the dextro-form only in the blue and perennial lupin.   It is obtained by extracting the dried ground seeds with alcohol containing 1 per cent. of hydrochloric acid.   The alcohol is distilled off and the residue heated with three times its volume of water.   The liquid is filtered free from fat, neutralised with caustic soda, and evaporated to a small volume, then made alkaline and the liberated alkaloid extracted with chloroform.   The residue left on distilling off the chloroform is made slightly acid with hydrochloric acid and evaporated to a thick syrup.   This on standing deposits crystals of d-lupanine hydrochloride, and when this has all been deposited the mother liquors yield a supply of i-lupanine hydrochloride.

i-Lupanine crystallises from light petroleum in needles, m.p. 99°. It is strongly alkaline and dissolves in all ordinary solvents.   The

[1] *Berichte*, 1902, **35**, 1914.
[2] Schmidt, *Arch. Pharm.* 1897, **235**, 192 ; Davis, *ibid*. 199, 218, 229. *Cf.* Soldaini, *ibid*. 1893, **231**, 321, 481.

hydrochloride, $B.HCl.2H_2O$, has m.p. 127°–128° or 250°–252° (dry), and the aurichloride, m.p. 177°–178° (decomp.), 200° (Beckel), is sparingly soluble in water.

d-*Lupanine* closely resembles the inactive alkaloid, but melts at 44°, $[\alpha]_D^{18} + 51\cdot5°$, and can be obtained from it by fractional crystallisation of the mixed thiocyanates formed from the racemic alkaloid. The hydrochloride, $B.HCl.2H_2O$, m.p. 127°, $[\alpha]_D + 62°$, and the hydrobromide, m.p. 111°–112°, are both less soluble than the corresponding salts of the inactive base. The aurichloride has m.p. 188°–189°, and the thiocyanate, m.p. 189°–190°.

l-*Lupanine*, obtained as described above by fractional crystallisation of the thiocyanate of the inactive form, melts at 43°–44°. The aurichloride has m.p. 188°–189° (decomp.).

With bromine d-lupanine furnishes a perbromide which on treatment with alcohol yields ethoxylupanine dihydrobromide, $C_{15}H_{23}ON_2.OC_2H_5.2HBr$.[1] Beckel [2] has compared the action of methyl iodide on d-lupanine and sparteine, and concludes that d-lupanine is not constituted similarly to sparteine.

Hydroxylupanine, $C_{15}H_{24}O_2N_2.2H_2O$, crystallises in rhombic prisms, m.p. 76°–77° or 172°–174° (dry), $[\alpha]_D + 64\cdot12°$, is soluble in water or alcohol, and yields crystalline salts. The aurichloride, $B.HAuCl_4$, m.p. 205°–206°, forms prisms from dry alcohol. On reduction with hydriodic acid the base yields d-lupanine.

In addition to these alkaloidal constituents, Schulze has shown that *Lupinus luteus* seedlings contain a series of amino-acids.[3]

Physiological Action of Lupin Alkaloids. The physiological action of sparteine is discussed at p. 124. Lupinine is only slightly toxic. The d- and i- forms of lupanine are said to be equally active physiologically. They are bitter to the taste and poisonous.

MITRAGYNE SPP.

Alkaloids have been found in a number of species belonging to this genus, e.g., *M. africana*, *M. parviflora*,[4] and from *M. speciosa* Miss Field [4] has isolated mitragynine and from *M. diversifolia*, mitraversine.

[1] Beckel, *Arch. Pharm.* 1912, **250,** 700. *Cf.* Soldaini, *Chem. Centr.* 1902 [i], 669 ; 1905 [i], 826 ; and Molander, *Ber. deut. Pharm. Ges.* 1921, 31, 265.

[2] *Arch. Pharm.* 1911, **249,** 329.

[3] *Zeit. physiol. Chem.* 1899, **28,** 465. *Cf.* Njegovan, *ibid.* 1911, **76,** 1.

[4] Hooper, *Pharm. Journ.* 1907, **78,** 453. *Cf.* Field, *Trans. Chem. Soc.* 1921, **119,** 887.

Mitragynine, $C_{22}H_{31}O_5N$, isolated as the picrate, has not been crystallised, but is obtained in solid crusts by distillation, m.p. 102°–106°, b.p. 230°–240°/5 mm. The hydrochloride forms rhomb-shaped leaflets, m.p. 243°, the acetate silky needles, m.p. 142°, and the picrate orange-red slender needles, m.p. 223°–224°. The alkaloid contains three methoxyl groups (two of which are present as $(.CO_2Me)$ and one as $(.OMe)$, but no methylimino group. It shows local anæsthetic action and is believed to be an indole derivative.

Mitraversine, $C_{22}H_{26}O_4N_2$ (?), m.p. 237° readily soluble in dilute caustic soda solution, yields a hydrochloride, rhomb-shaped leaflets, m.p. 208°–210°. The alkaloid contains two methoxyl groups.

NECTANDRIA RODIOEI (GREENHEART), *BUXUS SEMPERVIRENS* (BOXWOOD) AND " PAREIRA BRAVA "

The literature dealing with the alkaloids of these three plants presents one of the most tangled of the many tangled chapters of alkaloidal chemistry. In 1843, Maclagan isolated from greenheart bark the alkaloids bebeerine and sepeerine.[1] Later on Walz[2] asserted that Maclagan's bebeerine was identical with buxine, which Fauré[3] had obtained from boxwood in 1830. Flückiger[4] also took the view that buxine and bebeerine were identical and in addition showed that pelosine, which Wiggers[5] isolated from *Cissampelos Pareira* (one of the roots which appears in commerce as " Pareira brava ") and which Flückiger himself had also prepared from *Chondrodendron tomentosum* root (the true " Pareira brava ") was identical with bebeerine. Scholtz[6] has confirmed the statement that pelosine and bebeerine are identical, but believes that buxine is distinct from bebeerine. Meanwhile nothing further has been heard of three other alkaloids isolated from greenheart bark by Maclagan and Gamgee[7] in 1869, and the same applies to buxine and a series of other alkaloids which Barbaglia[8] obtained from boxwood, and to the sepeerine of Maclagan,[1] and that of Walz.[9]   Finally,

[1] *Annalen,* 1843, **43,** 106 ; 1845, **55,** 105.
[2] *Jahresberichte,* 1860, p. 548.
[3] *Jahresberichte Berz.* 1830, **11,** 245.
[4] *Pharm. Journ.* 1869–70 [ii], **11,** 192.
[5] *Annalen,* 1840, **33,** 81.
[6] *Berichte,* 1896, **29,** 2054 ; *Arch. Pharm.* 1898, **236,** 530 ; 1899, **237,** 199.
[7] *Pharm. Journ.* 1869–70 [ii], **11,** 19.
[8] *Gazzetta,* 1883, **13,** 249 ; *Berichte,* 1884, **17,** 2655.
[9] *Jahresberichte,* 1859, p. 565.

Faltis [1] and Neumann have made the disconcerting suggestions that the true source of " Pareira bark " root is *Chondrodendron platyphyllum*, the alkaloids it contains are different from those of greenheart bark, and that, in consequence, the alkaloids hitherto known as " bebeerines " should be called " chondodendrines." Much of the work done in recent years on these alkaloids has been carried out with commercial " bebeerine sulphate " made from " pareira bark," so that the following should be regarded as applying mainly to alkaloids presumed to be derived from this source. " Bebeerine sulphate " has been shown by the work of Scholtz and Faltis to consist of at least five alkaloids :

1. Bebeerine (Pelosine, α-Bebeerine, α-Chondodendrine).
2. *iso*Bebeerine (*iso*-Chondodendrine).
3. β-Bebeerine (β-Chondodendrine).
4. Bebeerine-β.
5. Chondrodine.

Bebeerine, $C_{18}H_{21}O_3N$ (*α-Chondodendrine*), crystallises from methyl alcohol in small prisms, m.p. 214°, $[\alpha]_D - 298°$. The hydrochloride, B.HCl, forms small needles, m.p. 259°–260° : the platinichloride is amorphous ; the methiodide, $B.CH_3I$, m.p. 268°–270°, and the monoacetyl and monobenzoyl derivatives, melting at 147°–148° and 139°–140° respectively, are crystalline.[2] Bebeerine contains one methoxyl group, a phenolic hydroxyl group and a methylimino group.[2]

Chondrodine, $C_{18}H_{21}O_4N$, amorphous, m.p. 218°–220°, $[\alpha]_D - 75°$ in alcohol. The hydrochloride, B.HCl, m.p. 274°–275°, forms yellow leaflets ; the picrate, m.p. 193°–194°, is a crystalline powder and the picrolonate, m.p. 185°–186°, forms greenish-yellow stellate clusters of needles. The alkaloid contains a methoxyl and a methylimino group, and yields a diacetyl- and a dibenzoyl-derivative, melting at 270° (*decomp.*) and 295° respectively. The diethyl ether hydrochloride, m.p. 258°, crystallises in yellow needles.[3]

*iso***Bebeerine,** $C_{18}H_{19}O_3N$, crystallises in rhombic needles, m.p. 290° (*decomp.*), $[\alpha]_D = 0$, and is regarded as a stereoisomeride of Scholtz's bebeerine.[4] According to Scholtz,[4] it melts at 297°, and

[1] *Monats.* 1921, **42,** 311.
[2] Scholtz, *Berichte,* 1896, **29,** 2054 ; *Arch. Pharm.* 1898, **236,** 530 ; 1906, **244,** 555.
[3] Scholtz, *Arch. Pharm.* 1911, **249,** 408.
[4] Faltis, *Monats.* 1912, **33,** 873. *Cf.* Scholtz, *Arch. Pharm.* 1913, **251,** 136 ; 1914, **252,** 513.

gives a crystalline hydriodide, m.p. 300° (*decomp.*), hydrochloride, and methiodide, B.MeI, large prismatic crystals, m.p. 275° (*decomp.*). On exhaustive methylation it yields in two stages trimethylamine and a non-nitrogenous product, $C_{18}H_{20}O_3$, rhombic leaflets or slender needles, m.p. 325°. On demethylation by boiling with hydrochloric acid the corresponding dihydric phenol *iso*bebeeridine, $C_{17}H_{17}O_3N$, is formed. This crystallises in microscopic yellow cubes, m.p. 238°–240°, yields crystalline salts and a methiodide, yellow needles, m.p. 262°–263°; it gives the same colour reactions as *iso*bebeerine.[1] At this stage Scholtz suggested that *iso*bebeerine probably had formula I or II, no position being assigned to the third oxygen atom, whilst Faltis[2] proposed III or IV, of which IV is supported by the

I   II
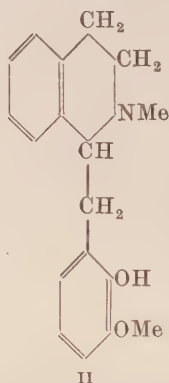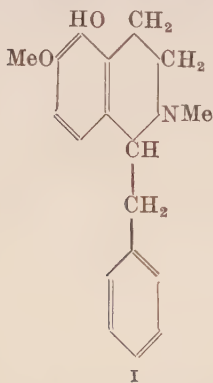
results of a study of exhaustive methylation products, and, in particular, of the final non-nitrogenous product, $C_{18}H_{18}O_3$ (*Cf.* Scholtz

V   III   IV
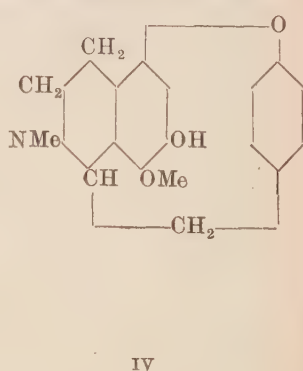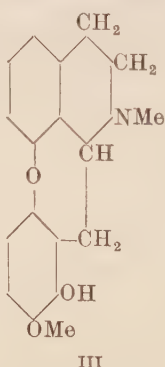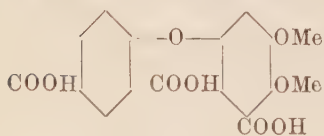
[1] Scholtz, *Arch. Pharm.* 1915, **253**, 622.
[2] Faltis and Neumann, *Monats.* 1921, **42**, 311 ; with Heczko, *ibid.* 1923, **43**, 377.

above), which on oxidation by permanganate gave a tricarboxylic acid, $C_{12}H_5O(OMe)_2.(COOH)_3$, m.p. $177\cdot5°$–$178°$. This on demethylation yielded the corresponding dihydroxy-acid (giving the colour reactions of a catechol derivative) which on fusion with potash yielded (1) *p*-hydroxybenzoic acid, and (2) a product which on methylation gave a trimethoxybenzoic acid in which the methoxyl groups are probably in positions $2:3:5$, and if so, the tricarboxylic acid may be represented by formula v.

β-**Bebeerine,** $C_{21}H_{23}O_4N$, is amorphous and yields amorphous salts. It has m.p. $142°$–$150°$, $[\alpha]_D^{21} + 28\cdot6°$ (in alcohol), or $-24\cdot7°$ (in pyridine). The reactions of the alkaloid indicate that it contains a hydroxyl, a methoxyl, and a methylimino group.[1] According to Scholtz,[1] it has the formula, $C_{18}H_{21}O_3N$, and yields a crystalline methiodide, $B.CH_3I$ (m.p. $80°$, hydrated), or $258°$–$259°$ (*dry, decomp.*).

Bebeerine-β, $C_{22}H_{23}O_5N$, a yellow powder, m.p. $220°$ (*decomp.*), $[\alpha]_D + 56\cdot7°$. Its reactions indicate the presence of the following groups, $C_{20}H_{15}O_2(NMe)(OH)_2(OMe)$. On fusion with potash protocatechuic acid is formed.[1]

Physiological Action. These three drugs are no longer used to any extent in medicine. Of the alkaloids occurring in them, " bebeerine " has been examined pharmacologically several times, and is supposed to have an action somewhat similar to that of quinine, but, as explained above, the name " bebeerine " has been applied to many different things, and the pharmacology as well as the chemistry of these alkaloids needs clearing up.

PHYSOSTIGMA VENENOSUM

The seeds of this plant (Calabar beans) have long been employed in West Africa by natives as an ordeal bean. They were first examined by Jobst and Hesse,[2] who isolated the alkaloid, physostigmine, in an amorphous condition, and subsequently by Vee, who obtained the same alkaloid in a crystalline state and named it eserine.[3] Since then Harnack and Witkowski announced a second alkaloid, CALABARINE,[4] which later investigators have shown to be a mixture of decomposition products. In 1888 Böhringer and

[1] Faltis, *Monats.* 1912, **33**, 873. *Cf.* Scholtz, *Arch. Pharm.* 1913, **251**, 136.

[2] *Annalen*, 1864, **129**, 115 ; 1867, **141**, 913.

[3] *Jahresberichte*, 1865, p. 456.

[4] *Arch. exp. Path. Pharm.* 1876, p. 401.

Söhne [1] obtained the crystalline alkaloid eseridine, $C_{15}H_{23}O_3N_3$, and Ehrenberg in 1893 [2] a third alkaloid, eseramine.   The next addition to this list was *iso*physostigmine, isolated by Ogui.[3]   Salway,[4] in 1911, recorded the presence of a fifth alkaloid, physovenine, and four years later Polonovski and Nitzberg isolated a new base geneserine.[5]

Estimation.   The following process is due to Salway : [6] 20 grm. of Calabar beans in No. 60 powder are mixed with 200 c.c. of ether and 10 c.c. of 10 per cent. sodium carbonate solution, and the whole shaken occasionally during four hours.   One hundred cubic centimetres of ether are withdrawn and $N/10$ sulphuric acid added in excess, and shaken.   The acid is withdrawn and the treatment repeated twice, using each time 10 c.c. of $N/10$ acid.   The combined acid liquids are make alkaline with 10 per cent. sodium carbonate solution and shaken with ether ten times, using 20 c.c. of ether each time.   The combined ethereal extracts are shaken once with 5 c.c. water, the ether solution separated and the solvent distilled off.   The residue is dissolved in 5 c.c. $N/10$ acid and titrated with $N/50$ alkali, using iodeosin as indicator.

Physostigmine (*Eserine*), $C_{15}H_{21}O_2N_3$.   It is best prepared by shaking with ether, in presence of excess of sodium carbonate, the water-soluble portion of an alcoholic extract of the beans.   The ethereal extract is then shaken out with dilute sulphuric acid until the acid is neutralised by the alkaloid, and from this solution the physostigmine is precipitated as the salicylate, from which it may be regenerated by shaking with a solution of sodium carbonate and extraction with ether.

Physostigmine crystallises in two forms, m.p. 86°–87° and m.p. 105°–106°, the latter being the more stable.   It dissolves easily in alcohol, ether, or chloroform ; the solutions are alkaline and lævorotatory, $[\alpha]_D - 75\cdot8°$ (in chloroform).   The hydrobromide, $B.2HBr$, forms colourless needles, m.p. 224°–226° (from alcohol).   The salicylate forms colourless acicular crystals, m.p. 186°–187°.   The sulphate, $B_2.H_2SO_4$, is a microcrystalline, deliquescent powder, m.p. 145° : the aurichloride, $B.2HAuCl_4$, yellow leaflets, m.p. 163°–165°, and platinichloride, $B.H_2PtCl_6$, orange-yellow needles, m.p. 180°.   The mercuric iodide derivative, $B.HI.HgI_2$, crystallises

[1] *Pharm. Post.* 1888, **21**, 663.
[2] *Verh. Ges. deut. Nat. Aertzte,* 1893, **11**, 102.
[3] *Apoth. Zeit.* 1904, **19**, 891.
[4] *Trans. Chem. Soc.* 1911, **99**, 2148.
[5] *Bull. Soc. Chim.* 1915 [iv], **17**, 244.
[6] *Amer. J. Pharm.* 1912, **84**, 49.

in small prisms, m.p. 170°, the benzoate forms prisms, m.p. 115°–116°, and the picrate crystallises from dilute alcohol in yellow feathery needles, m.p. 114°.

Physostigmine and its salts dissolve in nitric acid, forming a yellow solution, which on warming becomes red, and on evaporation to dryness leaves a green residue.   A neutral solution of the sulphate gives with excess of ammonia a white precipitate, which gradually becomes pink and dissolves in excess of the alkali, forming a reddish solution which eventually becomes yellowish-green.

Physostigmine behaves as a monoacidic, tertiary base.   On treatment with alkali or when heated alone *in vacuo*, it is converted into ESEROLINE, $C_{13}H_{18}ON_2$, methylamine and carbon dioxide, the two latter products being derived from a urethane group in the parent alkaloid.[1]   With sodium ethoxide the products are eseroline and methylurethane, whilst if the alkaloid be heated at its melting-point, methylcarbimide, $CONHMe$, is evolved.   Eseroline can be reconverted to physostigmine by the action of methylcarbimide in ether in presence of sodium and using other carbimides homologues of physostigmine have been prepared.[2]   Eseroline forms colourless needles from benzene, m.p. 129°, $[\alpha]_D - 107°$ (in alcohol), and like physostigmine behaves as a monoacidic tertiary base ; it contains one methylimino group.[3]   On exposure to air it undergoes oxidation to RUBRESERINE, $C_{13}H_{16}O_2N_2 . H_2O$, crystallising from water in deep red needles, m.p. 152° (*dry*), and under certain conditions to ESERINE BLUE, $C_{17}H_{23}O_2N_3$, which appears to be a combination of eseroline with one of the degradation products resulting from the oxidation (Salway).[1]   Eseroline forms a methiodide, which, on heating at 200° in an atmosphere of carbon dioxide, is converted into a phenolic substance, $C_{10}H_{11}ON$, colourless needles, m.p. 103°, which has been called   physostigmol,   and   probably   has   the   constitution

$$HO.C_6H_3 \left\langle \begin{array}{c} NMe— \\ CMe— \end{array} \right\rangle CH \quad \text{(Straus).[1]}$$

The HO group is, as shown,
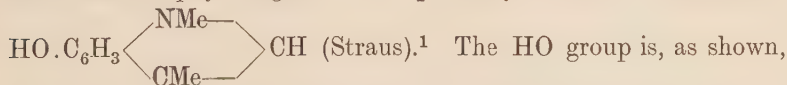
phenolic, and methyl and ethyl ethers of physostigmol can be prepared.   A more detailed study of the treatment of eserine and its

[1] Petit and Polonovski, *Bull. Soc. chim.* 1893 [iii], **9**, 1008 ; 1915 [iv], **17**, 235 ; Ehrenberg, *Verh. Ges. deut. Nat. Aerzte*, 1893 [ii], 102. *Cf.* Salway, *Trans. Chem. Soc.* 1912, **101**, 978 ; and Straus, *Annalen*, 1913, **401**, 350 ; 1914, **406**, 332.

[2] Polonovski and Nitzberg, *ibid.* 1916 [iv], **19**, 27, 46.

[3] Straus, *loc. cit.* found two such groups.   *Cf.* however, Herzig and Lieb, *Monats.* 1918, **39**, 285.

ethyl ether (eserethole) with methyl iodide has been made by Barger and Stedman,[1] who show that as many as five molecules of methyl iodide may be taken up in this way, leading probably to far-reaching changes in the constitution of the substance.

On distillation with zinc dust, physostigmine yields 2-methyl-indole with a small amount of 1-methylindole,[2] and all recent investigators have worked on the assumption that the alkaloid has an indole nucleus, and Straus [3] has suggested a constitution for eseroline based on this view, which represents it as a hydroxydi-N-methylhexahydronorharman.

Geneserine, $C_{15}H_{21}O_3N_3$, was obtained by Polonovski and Nitzberg [4] by extracting calabar beans previously soaked in 2 per cent. sodium hydroxide solution with ether.   It forms orthogonal crystals, m.p. 128°–129°, $[\alpha]_D$ — 175° (in alcohol), — 188° (in dilute sulphuric acid).   It is a weak base, does not give crystalline salts with mineral acids, but yields a salicylate, m.p. 89°–90°, picrate, m.p. 175°, and a methiodide, m.p. 215°.   At 160° it gives off methylcarbimide and is decomposed by sodium in alcohol, furnishing GENESEROLINE, $C_{13}H_{18}O_2N_2$, which is completely analogous with eseroline, similarly formed from physostigmine, and, like it, yields methyl and ethyl ethers, $e.g.$, the ethyl ether, genestherole, is obtained by the action of ethyl bromide on geneseroline in presence of sodium ethoxide. Geneserine differs from physostigmine by one atom of oxygen, shows a fairly complete parallelism in its reactions and is reduced to physostigmine by zinc dust and acetic acid in alcohol, whilst physostigmine can be oxidised by hydrogen peroxide to geneserine.   On these grounds Polonovski [5] regards it as an amine oxide of physostigmine, its relations to the latter being as follows :

$$NMe : C_{12}H_{14}N.O.CO.NHMe \qquad O : NMe : C_{12}H_{14}N.O.CO.NHMe$$
$$\textit{Physostigmine} \qquad\qquad \textit{Geneserine}$$
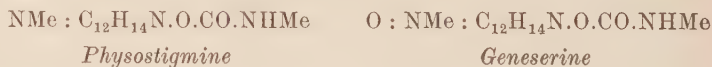
Eseramine, $C_{16}H_{25}O_3N_4$, was first obtained by Ehrenberg,[6] and

[1] $Trans.$ $Chem.$ $Soc.$ 1921, **119,** 891 ;   1923, **123,** 759.   Cf. M. and M. Polonovski, $Compt.$ $rend.$ 1923, **176,** 1480, 1813 ; **177,** 127 ; $Bull.$ $Soc.$ $Chim.$ 1923 [iv], **33,** 970, 977.
[2] Salway, $Trans.$ $Chem.$ $Soc.$ 1912, **101,** 988.
[3] $Annalen$, 1913, **401,** 350 ; Cf. Barger and Stedman, $Trans.$ $Chem.$ $Soc.$ 1923, **123,** 758 ;   Salway, $ibid.$ 1913, **103,** 352 ; M. and M. Polonovski, $Compt.$ $rend.$ 1923, **176,** 1896.
[4] $Bull.$ $Soc.$ $chim.$ 1915 [iv], **17,** 244.
[5] $Ibid.$ 1917 [iv], **21,** 191 ;   1918 [iv], **23,** 335, 356.
[6] $Verh.$ $Ges.$ $deut.$ $Nat.$ $Aerzte$, 1893, **11,** 102.

its occurrence in Calabar beans has been confirmed by Salway.[1] It remains in the ethereal liquid after physostigmine has been extracted by dilute sulphuric acid (p. 416), and may be obtained by treating the residue with a small quantity of ether, when it forms a granular powder, which on recrystallisation from alcohol forms colourless needles, m.p. 245° (*decomp.*). It is sparingly soluble in ether, chloroform, or benzene, but readily in hot alcohol.

*iso*Physostigmine, $C_{15}H_{21}O_2N_3$, obtained by Ogui,[2] is insoluble in ether and furnishes a crystalline sulphate, m.p. 200°–202°. Salway was unable to confirm its occurrence in Calabar beans.[1]

Eseridine, $C_{15}H_{23}O_3N_3$, was obtained by Böhringer and Söhne [3] and subsequently examined by Eber.[4] It is stated to melt at 132° and to be converted into physostigmine when heated with dilute mineral acids. Salway [1] was unable to obtain any evidence of the presence of escridine in Calabar beans.

Physovenine, $C_{14}H_{18}O_3N_2$, was obtained by Salway [1] from the mother liquors left after the separation of eseramine (*see* p. 418). It crystallises from a mixture of benzene and light petroleum in small colourless prisms, m.p. 123°, is very soluble in alcohol, benzene, or chloroform, less so in ether, but insoluble in water or light petroleum. Its salts are dissociated by water. With barium hydroxide, physovenine liberates carbon dioxide and assumes a deep red colour, and owing to the similarity of this behaviour with that of physostigmine, Salway suggests that physovenine may be an intermediate product in the formation of eseroline from physostigmine, thus :

$$C_{15}H_{21}O_2N_3 + H_2O = C_{14}H_{18}O_3N_2 + CH_3.NH_2$$
Physostigmine   *Physovenine*

$$C_{14}H_{18}O_3N_2 = C_{13}H_{18}ON_2 + CO_2$$
Physovenine   *Eseroline*
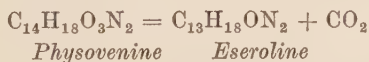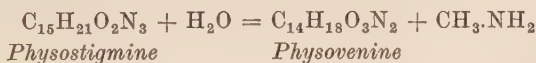
Physiological Action. Physostigmine is intensely poisonous, causing depression of the central nervous system, with death from failure of respiration due to paralysis of the medullary centre. In many respects it resembles pilocarpine and muscarine in its physiological action, causing, for example, powerful contractions of the stomach and intestine, and increasing the activity of the secretory glands. Physostigmine is principally used in ophthalmic medicine

[1] *Trans. Chem. Soc.* 1911, **99**, 2148.
[2] *Apoth. Zeit.* 1904, **19**, 891.
[3] *Pharm. Post.* 1888, **21**, 663.
[4] *Pharm. Zeit.* 1892, **37**, 483.

on account of its property of contracting the pupil of the eye (myosis), either when applied locally or administered internally. Physostigmine is excreted in the urine mainly and appears in it a few minutes after injection.

Harnack's " calabarine," the existence of which has not been confirmed, was antagonistic to physostigmine, and resembled atropine in its general action.

Eseridine (see p. 419) is stated to exert the same kind of action as physostigmine, but to be much less poisonous. Eseramine and *iso*physostigmine have not been fully examined physiologically. Physovenine appears to be at least as poisonous as physostigmine. Rubreserine (p. 417) is inactive.[1]   Geneserine is not myotic and has generally a much weaker action than physostigmine and is less toxic.[2]

PSYCHOTRIA IPECACUANHA

The roots of this plant constitute the Brazilian ipecacuanha of commerce and probably also that obtained from Johore in Malaya. A second commercial variety (Carthagena ipecacuanha) is believed to be derived from *P. acuminata* collected in Colombia.   Emetine, the principal alkaloid of this drug, was first obtained by Pelletier and Magendie [3] in 1817, but was prepared for the first time in a pure state by Paul and Cownley,[4] who separated from commercial emetine the phenolic base, cephæline, and later obtained a third alkaloid psychotrine. To these Pyman [5] added emetamine and *O*-methylpsychotrine, in 1917. Brazilian roots contain up to 2·5 per cent. of total alkaloids, of which about 70 per cent. is said to be emetine, whilst Carthagena roots yield about 2·0 per cent. of alkaloids of which less than half is emetine.   From roots yielding 2·7 per cent. of total alkaloids, Carr and Pyman [6] isolated 1·35 per cent. of emetine and 0·25 per cent. of cephæline, both alkaloids being pure.   The amount of emetamine varies according to Pyman [7] from 0·002 to 0·006 per cent. and of *O*-methylpsychotrine from 0·015 to 0·033 per cent.

    [1] Heubner, *Chem. Soc. Abstr.* 1905 [ii] 487.
    [2] Polonovski and Combemale, *Compt. rend. Soc. biol.* 1923, **88**, 881.
    [3] *Ann. Chim. Phys.* 1817 [ii], **4**, 172 ; 1823 [ii], **24**, 180.
    [4] *Pharm. Journ.* 1894–95 [iii], **25**, 111, 373, 641, 690 ; 1896 [iv], **2**, 321 ; 1898 [iv], **7**, 100.   *Cf.* Glenard, *Ann. Chim. Phys.* 1876 [v], **8**, 277, and Kunz-Krause, *Arch. Pharm.* 1887, **225**, 461 ; 1894, **232**, 466.
    [5] *Trans. Chem. Soc.* 1917, **111**, 428.
    [6] *Ibid.* 1914, **105**, 1599.   *Cf. Proc. Chem. Soc.* 1913, **29**, 226 ; and Hesse, *Annalen*, 1914, **405**, 1.
    [7] *Trans. Chem. Soc.*, 1917, **111**, 428.

The alkaloids may be prepared by extracting the ground roots with alcohol, concentrating the extract, diluting with water and shaking out with ether to remove fat, resin, etc.   The clear liquor is then made alkaline with ammonia and the alkaloids removed by means of ether or chloroform.   From this solvent cephæline may be extracted by agitation with caustic soda solution and then emetine by shaking with acid.

Estimation of Alkaloids.   The British Pharmacopœia, 1914, gives the following process for the estimation of the ether-soluble alkaloids in ipecacuanha :   Seven grammes of root in No. 60 powder are shaken frequently during five minutes with 70 c.c. of a mixture of chloroform (1 vol.) and ether (3 vols.), after which 5 c.c. of dilute ammonia solution are added and the mixture shaken frequently during one hour.   Enough water (about 5 c.c.) is then added to make the powder agglomerate on shaking violently, and 50 c.c. of the clear liquid are separated and shaken with ten c.c. of $N/10$ hydrochloric acid, finally with three lots of water of 3 c.c. each.   The combined acid and water extract is made alkaline with ammonia solution and the alkaloids removed by shaking first with 10 c.c. of a mixture of chloroform (1 vol.), ether (6 vols.), and then with three portions (each of 5 c.c.) of the same mixture.   The ethereal solutions are mixed, the solvent distilled off, and the residue dried at 80° and weighed.   It should be not less than 0·100 grm. = 2 per cent. of alkaloids.

The United States Pharmacopœia (9th Rev.), uses a process identical with that prescribed for belladonna root (*see* p. 65) with the following alterations :   Ten grammes of root are used in No. 80 powder in a 250 c.c. flask with 100 c.c. of ether.   Fifty cubic centimetres of the ethereal extract (= 5 grm. of root) are taken to complete the assay, ether being used instead of chloroform for the final shaking out.   The alkaloidal residue is dissolved in 10 c.c. of $N/10$ sulphuric acid for final titration and each cubic centimetre of $N/10$, H_2SO_4 used = 0·024 grm. of ether-soluble alkaloids.

Emetine, $C_{29}H_{40}O_4N_2$.   Though emetine had been frequently investigated since its discovery in 1811, it was only in 1913 that it and its principal salts were carefully and systematically characterised by Carr and Pyman.[1]   It forms a white amorphous powder, m.p. 74°, $[\alpha]_D$ — 25·8° to 32·7° (in 50 per cent. alcohol, $c = 1·805$ to 4·118) or — 50° (in chloroform), readily soluble in alcohol, ether or chloroform,

[1] *Proc. Chem. Soc.* 1913, **29**, 226 ;   *Trans. Chem. Soc.* 1914, **105**, 1599.   *Cf.* Hesse, *Pharm. Journ.* 1898 [iv], **7**, 98 ;   *Annalen*, 1914, **405**, 1.

less so in benzene or light petroleum, and sparingly in water. The hydrochloride, $B.2HCl.7H_2O$,[1] separates from hot water in colourless woolly needles or from cold saturated solutions in thick transparent prisms, m.p. 235°–255° (dry, decomp.),[2] $[\alpha]_D + 11°$ to $+ 21°$ (in water $c = 1$ to 8), $+ 53°$ (in chloroform). The hydrobromide, $B.2HBr.4H_2O$, separates from water in long slender colourless needles, m.p. 250°–260°, $[\alpha]_D + 12°$ to 15·2° (in water, $c = 1·4$ to 3·9). The hydriodide is sparingly soluble in water, and crystallises from alcohol in colourless needles, $B.2HI.3H_2O$, m.p. 235°–238°. The nitrate, $B.2HNO_3.3H_2O$, crystallises from alcohol or water in rosettes of silky needles, sinters at 188°, and gradually melts up to 245°. The sulphate forms white woolly needles, $B.H_2SO_4.7H_2O$, m.p. 205°–245°, and is very soluble in water. The platinichloride is amorphous, m.p. 253°–265°.

Cephæline, $C_{28}H_{38}O_4N_2$, is best purified by recrystallising from ether, the base regenerated from a pure salt such as the hydrochloride, or hydrobromide. It forms colourless needles, m.p. 115°–116° or (after drying at 100°) 120°–130°, $[\alpha]_D - 43·4°$ (in chloroform), is readily soluble in chloroform or alcohol, less so in ether, insoluble in water, but soluble in alkali.[3] The hydrochloride, $B.2HCl.7H_2O$, crystallises from dilute hydrochloric acid in stout granular prisms, m.p. 245°–270°, $[\alpha]_D + 25°$ to 29·5° (in water, $c = 1·7$ to 6·7). An acid hydrochloride, $B.5HCl$, m.p. 84°–86°, separates in fine needles from strongly acid solutions. The hydrobromide, $B.2HBr.7H_2O$, forms from dilute hydrobromic acid, colourless prisms, m.p. 266°–293°. The sulphate, hydriodide and nitrate, are amorphous.[3]

Psychotrine, $C_{28}H_{36}O_4N_2.4H_2O$, may be obtained by extracting the mother liquors left from the separation of emetine and cephæline with chloroform. It is best recrystallised from moist acetone or alcohol, and then forms large yellowish prisms, showing a pale blue fluorescence. After drying at 100° it sinters at 120°, and flows at 138°. It is sparingly soluble in water, ether, or benzene, more so in acetone, chloroform, or alcohol. The hydriodide, $B.2HI$, separates from dilute hydriodic acid in microscopic yellow needles, m.p. 200°–222°; the nitrate crystallises from water in silky colour-

[1] Cf. Paul and Cownley, Pharm. Journ. 1894 [iii], **25**, 373 ; Keller, Arch. Pharm. 1911, **249**, 519.

[2] The melting-points of the ipecacuanha alkaloids and their salts are often indefinite ; the first temperature mentioned is usually a sintering-point, and the second the point at which the substance flows or decomposes.

[3] Carr and Pyman, Trans. Chem. Soc. 1914, **105**, 1608. Cf. Hesse, Annalen, 1914, **405**, 1.

less needles, $B.2HNO_3.H_2O$, m.p. 184°–187° (dried at 100°). The sulphate, $B.H_2SO_4.3H_2O$, is very soluble in water, but can be crystallised from it in faintly yellow, shining scales, m.p. 214°–217° (dried at 100°), $[\alpha]_D + 39.2°$ (in water, anhydrous salt).[1]

O-Methylpsychotrine, $C_{29}H_{38}O_4N_2$. This alkaloid was isolated by Pyman [2] from the non-phenolic portion (emetine fraction) of the total alkaloids of all the commercial varieties of ipecacuanha by removing the emetine as hydrobromide, regenerating the bases remaining in the mother liquors and converting them into hydrogen oxalates when these salts of O-methylpyschotrine and emetamine crystallise together. This mixture is then separated by taking advantage of the fact that methylpsychotrine is removed first by dilute sulphuric acid from a solution of the two bases in chloroform. For details of the method the original paper should be consulted. The alkaloid has not been obtained crystalline ; it is dextrorotatory, $[\alpha]_D + 43.9°$ to 46.1° (in alcohol, $c = 3.9$ to 2.1). Dilute aqueous solutions of the salts are fluorescent. The sulphate, $B.H_2SO_4.7H_2O$, separates from water in large, hard, triboluminescent prisms ; it melts at 247° (*decomp.*), after dehydration at 160°–170°, and has $[\alpha]_D + 54.1°$ (anhydrous salt, in water) ; a monohydrate, $B.H_2SO_4.H_2O$, is obtained by crystallisation from dry alcohol. The hydrobromide, $B.2HBr.4H_2O$, forms pale yellow silky needles, m.p. 190°–200° (dried *in vacuo*), $[\alpha]_D + 48.0°$ (anhydrous salt, in water). The hydrogen oxalate, $B.2H_2C_2O_4.3\frac{1}{2}H_2O$, m.p. 150°–162° (*decomp.*), $[\alpha]_D + 45.9°$ (anhydrous salt, in water), crystallises in rosettes of needles. The base, like emetine and cephæline, gives a green colour with Fröhde's reagent.

Emetamine, $C_{29}H_{36}O_4N_2$, crystallises from ethyl acetate in colourless needles, m.p. 155°–156°, $[\alpha]_D + 9.9°$ to 11.2° (in chloroform, $c = 6.14$ to 4.2), is insoluble in water or alkalis, readily soluble in alcohol, benzene or chloroform, sparingly in ether. The hydrobromide, $B.2HBr.7H_2O$, forms glistening prismatic needles from alcohol, m.p. 210°–225°, $[\alpha]_D - 24.3°$ to $- 22.0°$ (in water, $c = 8.04$ to 4.15). The hydrogen oxalate, $B.2H_2C_2O_4.3H_2O$, crystallises in colourless rosettes of needles, m.p. 165°–171° (dried *in vacuo*), $[\alpha]_D - 6.0°$ (in water). The alkaloid contains four methoxyl groups,

[1] Carr and Pyman, *Trans. Chem. Soc.* 1914, **105**, 1608. *Cf.* Hesse, *Annalen*, 1914, **405**, 1.
[2] Pyman, *Trans. Chem. Soc.* 1917, **111**, 431. Two other minor alkaloids of ipecacuanha, *ipecamine* and *hydroipecamine,* have been described by Hesse (*Annalen*, 1914, **405**, 1), and are discussed by Pyman, *loc. cit.* p. 421.

no methylimino group, and is not acted upon by benzoic anhydride, so that both nitrogen atoms appear to be tertiary. On reduction with sodium in alcohol it yields a phenolic and a non-phenolic base, and the latter, on benzoylation, yields benzoyl*iso*emetine, whence it appears probable that emetamine differs from emetine in containing two unsaturated linkages.[1] It gives an emerald-green colour with Fröhde's reagent.

Interrelationships of the Ipecacuanha Alkaloids. Examination of the empirical formulæ of the ipecacuanha alkaloids indicates that they are probably closely related :

$$\text{Psychotrine, } C_{28}H_{36}O_4N_2.$$
$$O\text{-Methylpsychotrine, } C_{29}H_{38}O_4N_2.$$
$$\text{Emetine, } C_{29}H_{40}O_4N_2.$$
$$\text{Cephæline, } C_{28}H_{38}O_4N_2.$$
$$\text{Emetamine, } C_{29}H_{36}O_4N_2.$$

Pyman [2] has shown that psychotrine on treatment with methyl sulphate in presence of sodium amyl oxide is converted into *O*-methylpsychotrine, and Carr and Pyman [2] that psychotrine on reduction gives a mixture of cephæline and *iso*cephæline (colourless, diamond-shaped plates, m.p. 159°–160°, $[\alpha]_D - 71 \cdot 8°$ (in chloroform). These are probably stereoisomerides, and on methylation with sodium methyl sulphate in presence of sodium amyl oxide yield, respectively, emetine and *iso*emetine,[3] ($C_{29}H_{40}O_4N_2.H_2O$, plates of radiating needles from ether, m.p. 97°–98°, $[\alpha]_D - 47 \cdot 4°$ in chloroform, salts dextrorotatory), the two latter being also producible (along with a third base, $C_{28}H_{38}O_3N_2$) by the reduction of *O*-methylpsychotrine,[3] whilst *iso*emetine appears to be one of the reduction products of emetamine (Pyman).[2] These interconversions, it will be seen, are mainly brought about by the addition of hydrogen or by methylation of hydroxy groups, and the interrelationships they imply may be graphically represented thus :

Cephæline	←	*Psychotrine*	→	iso*Cephæline*
$C_{25}H_{28}N_2(OCH_3)_3OH$		$C_{25}H_{26}N_2(OCH_3)_3OH$		$C_{25}H_{28}N_2(OCH_3)_3OH$
↓		↓		↓
Emetine	←	*O-Methylpsychotrine*	→	iso*Emetine*
$C_{25}H_{28}N_2(OCH_3)_4$		$C_{25}H_{26}N_2(OCH_3)_4$		$C_{25}H_{28}N_2(OCH_3)_4$
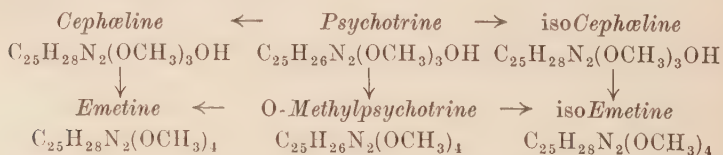
On hydrolysis by boiling with hydrochloric acid emetine and

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[1] Pyman, *Trans. Chem. Soc.* 1917, **111**, 442.
[2] *Trans. Chem. Soc.* 1917, **111**, 438. *Cf.* Carr and Pyman, *ibid.* 1914, **105**, 1624 ; and Karrer, *Berichte*, 1916, **49**, 2057.
[3] *Ibid.* 1918, **113, 224.**

cephæline evolve four and three molecules of methyl chloride respectively, and yield the same phenolic base (noremetine, norcephæline, emetoline (Karrer), $C_{25}H_{32}O_4N_2$, which gives the catechol reaction with ferric chloride.[1] None of the five alkaloids contains a methylimino group, and in all of them one nitrogen is secondary and the other tertiary, except in emetamine, where both are tertiary.

Methylation of the Alkaloids. When cephæline is treated with methyl sulphate or sodium methyl sulphate under various conditions, there is formed in addition to emetine (which was first shown to be the methyl ether of cephæline and partially synthesised in this way by Carr and Pyman in 1913),[2] more or less *N*-methylcephæline (wedge-shaped plates, m.p. 194°–195°, from dry alcohol), and *N*-methylemetine. The last-mentioned substance is also obtained by direct methylation of emetine ;[2] it has not been obtained crystalline, but yields a hydrobromide, $C_{30}H_{42}O_4N_2.2HBr.3H_2O$, m.p. 210°–230°, $[\alpha]_D + 5.6°$ (in water), crystallising in prismatic needles : the rotation of the free base in chloroform is $- 52.6°$.

When emetine is fully methylated with methyl iodide, it yields a mixture of α- and β-*N*-methylemetine methiodides, $C_{32}H_{48}O_4N_2I$, melting at 225°–226° and 262° respectively, both of which yield the same *N*-methylemetinemethine, $C_{32}H_{46}O_4N_2$ (oxalate, $B.H_2C_2O_4.$ $7\frac{1}{2}H_2O$, hard, brilliant prisms, m.p. 82°–83°),[3] so that the methiodides appear to be stereoisomeric.

N-Methyl*iso*emetinemethine, similarly obtained from *iso*emetine,[3] gives an oxalate, $C_{32}H_{46}O_4N_2.H_2C_2O_4.4H_2O$, crystallising in diamond-shaped prisms, m.p. 133°–134° (dried at 100°), $[\alpha]_D + 4.2°$ in water, and a methiodide,[3] which crystallises (with 1 mol. of methyl iodide) from water in silky needles, m.p. 178°–180°.

Oxidation. On gentle oxidation, for example, with iodine (1 mol.) in alcohol, emetine and *iso*emetine, $C_{29}H_{40}O_4N_2$, are converted into *O*-methylpsychotrine,[4] $C_{29}H_{38}O_4N_2$, whilst more vigorous oxidation of any of these three bases, for example, with four molecular proportions of iodine, or by boiling with ferric chloride yields a new monoacidic base, RUBREMETINE, $C_{29}H_{32}O_4N$, which has so far only been obtained in the form of its salts ; the hydrochloride, $B.HCl.6H_2O$,

[1] *Trans. Chem. Soc.* 1917, **111**, 438.   *Cf.* Carr and Pyman, *ibid.* 1914, **105**, 1624 ; and Karrer, *Berichte*, 1916, **49**, 2057.
[2] Carr and Pyman, *Trans. Chem. Soc.* 1914, **105**, 1615.   *Cf.* Pyman, *ibid.* 1917, **111**, 420.
[3] Pyman, *Trans. Chem. Soc.* 1917, **111**, 445 ; 1918, **113**, 234.   *Cf.* Karrer, *Berichte*, 1916, **49**, 2057 ; and Hesse, *Annalen*, 1914, **405**, 1.
[4] Pyman, *Trans. Chem. Soc.* 1917, **111**, 423.

brilliant scarlet needles, m.p. 127°–128°, or (after drying at 100°) 166°–173° ; like emetine, it gives a green colour with Fröhde's reagent.   When emetine is oxidised with permanganate in acetone, action proceeds much further, but the only definite product isolated so far is 6 : 7-dimethoxy*iso*quinoline-1-carboxylic acid.[1]

Emetine is used in medicine as an emetic, and, in small doses, as an expectorant and diaphoretic, but its principal use is in the form of emetine bismuthous iodide as a remedy for amœbic dysentery, owing to its specific toxic action on *Entamœba histolytica*.   None of the substances so far prepared from emetine or the allied alkaloids, *e.g.*, methylemetine, show any therapeutical advantage over emetine itself ; it is of interest that the stereoisomeride *iso*emetine is only half as toxic to rabbits as emetine, and exerts no emetic action in cats, but unfortunately it has no action on amœbæ.[2]   Most of the pharmacological work recorded on emetine was done with emetine, which probably contained cephæline, since it is only in recent years that the pure alkaloid has been available.   The minimum lethal dose of emetine for rabbits is about 4·0 milligrammes per kilogramme. Cephæline is more and psychotrine less toxic than emetine.

SENECIO SPP.

A number of plants of this genus, to which the " common groundsel " (*Senecio vulgaris*) belongs, are known to be poisonous, and from three of them alkaloidal constituents have been isolated, viz., *S. vulgaris*, *S. latifolius* DC., and *S. Jacobœa*.   The two latter are the cause of a peculiar liver disease in cattle and horses in South Africa and elsewhere, and this has been traced to chronic poisoning by the alkaloids they contain.[3]

Senecio latifolius DC.   This plant was investigated by Watt [4] and shown to contain two poisonous alkaloids, senecifoline and senecifolidine.   In the plant before flowering the alkaloids amount to 1·20 per cent., but after flowering to only 0·49 per cent.   The crude alkaloidal residue is separated into its two components by neutralising with dilute nitric acid and evaporating *in vacuo*, when senecifoline nitrate crystallises out, leaving senecifolidine nitrate in solution.

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[1] Carr and Pyman, *Trans. Chem. Soc.* 1914, **105,** 1597.   *Cf.* Windaus and Hermanns, *Berichte,* 1914, **47,** 1470.
[2] Dale and Low, quoted by Pyman, *Trans. Chem. Soc.* 1918, **113,** p. 224.
[3] *Bull. Imp. Inst.* 1911, **9,** 346.
[4] *Trans. Chem. Soc.* 1909, **95,** 466.

Senecifoline, $C_{18}H_{27}O_8N$, crystallises from chloroform, on adding light petroleum, in colourless rhombic plates, m.p. 194°–195° (*decomp.*), $[\alpha]_D + 28°\ 8'$ in alcohol, and is soluble in alcohol, ether, or chloroform, but insoluble in light petroleum or water. The nitrate forms rhombic prisms, m.p. 240° (*decomp.*), and, like all the salts, is lævorotatory, $[\alpha]_D - 15°\ 48'$ in water; the hydrochloride forms slender needles, m.p. 260° (*decomp.*), $[\alpha]_D - 20°$, and the aurichloride, $B.HAuCl_4.C_2H_5OH$, m.p. 220° (*dry*), crystallises from alcohol in golden-yellow, lath-shaped forms. On treatment with sodium hydroxide in alcohol, senecifoline is hydrolysed into senecifolic acid, $C_{10}H_{16}O_6$, and senecifolinine, $C_8H_{11}O_2N$. The former is probably a cyclic dihydroxydicarboxylic acid. Senecifolinine has only been obtained in the form of its salts; the hydrochloride separates from dry alcohol in rhombic prisms, m.p. 168°, $[\alpha]_D - 12°\ 36'$, and the aurichloride forms rhombic prisms, m.p. 150°, from alcohol.

Senecifolidine, $C_{18}H_{25}O_7N$, crystallises from dry alcohol in colourless, rhombic plates, m.p. 212° (*decomp.*), $[\alpha]_D^{20} - 13°\ 56'$ (in alcohol), and is less soluble in chloroform, ether, or alcohol than senecifoline. The nitrate, $(B.HNO_3)_2.C_2H_5OH$, is readily soluble in water or dry alcohol and crystallises from the latter on addition of ether in acicular prisms, m.p. 145°, $[\alpha]_D - 24°\ 21'$, containing alcohol: the aurichloride, $B.HAuCl_4$, separates from dry alcohol in golden-yellow, hair-like needles.

Both these alkaloids are bitter, and, according to Cushny, induce hepatic cirrhosis when administered to animals.[1]

Senecio Jacobœa. From this plant Watt has isolated a crystalline alkaloid which has not yet been fully described.[1]

Senecio vulgaris

Senecionine, $C_{18}H_{25}O_6N$, was obtained from *Senecio vulgaris* by Grandval and Lajoux,[2] together with a second amorphous alkaloid, SENECINE, of unknown composition. Senecionine crystallises from dry alcohol in rhombic tablets, $[\alpha]_D - 80\cdot49°$, is soluble in chloroform and slightly so in ether. No crystalline salts have been obtained.

SOLANUM SPP.

Among the Solanum species that have been chemically examined are *Solanum nigrum* (woody nightshade), *S. tuberosum* (potato),

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[1] *Proc. Roy. Soc.* 1911, B, **84**, 188. *Cf. Journ. S. African Med. Research*, 1920, **18**, 346; *Nature*, December 16, 1920, p. 503; *Lancet*, October 23, 1920, p. 848; November 27, p. 1089; December 18, p. 1266.
[2] *Compt. rend.* 1895, **120**, 1120.

S. lycopersicum, Linn. (tomato), *S. Dulcamara* (bittersweet), *S. cheno-podinum*, *S. verbascifolium*, *S. angustifolium*, and *S. sodomeum*. From most of these an alkaloidal glucoside, which was first prepared by Desfosses,[1] has been obtained. This substance has been named " solanine," but it is by no means certain that all these plants contain the same solanine, or that in most cases the solanine has been obtained in a pure state.

Firbas showed that probably at least two of these alkaloidal glucosides occur in this group of plants, viz., solanine, $C_{52}H_{93}O_{18}N$. $4\frac{1}{2}H_2O$, and solaneine, $C_{52}H_{83}O_{13}N.3\frac{3}{4}H_2O$, and that these may be accompanied by the basic decomposition product of solanine, viz. solanidine, $C_{40}H_{61}O_2N$.[2]   Firbas's formulæ for solanine and solanidine have been confirmed by Wittmann,[3] though Cazeneuve and Breteau [4] have suggested the simpler formula, $C_{28}H_{47}O_{11}N.2H_2O$ for solanine, and others have been put forward by Davis [5] and by Colombano, viz., $C_{32}H_{51}O_{11}N$.[6]

Solanine, $C_{52}H_{93}O_{18}N.4\frac{1}{2}H_2O$ (Firbas), $C_{28}H_{47}O_{11}N.2H_2O$ (Cazeneuve and Breteau), $C_{42}H_{75}O_{12}N$ (Davis), $C_{32}H_{51}O_{11}N$ (Colombano), forms colourless, slender needles, m.p. 244° (Firbas), 250° (Cazeneuve and Breteau), 235° (Davis), $[\alpha]_D^{20} - 42.16°$, almost insoluble in water, readily soluble in hot alcohol, but insoluble in ether or chloroform.   The alkaloid has a bitter taste and is hardly alkaline to litmus.   It dissolves in nitric acid with a yellow colour which slowly turns red, and gives a red colour with a mixture of sulphuric acid and sodium sulphate, and a green tint with sulphuric acid in alcohol.   The salts are amorphous and gummy.   According to Heiduschka and Sieger,[7] the hydrochloride is crystalline, m.p. 212° (*decomp.*).   Solanine is unaffected by alkalis, but when warmed with acids is hydrolysed into solanidine and a mixture of sugars including dextrose, rhamnose, and galactose.[8]

SOLANIDINE, $C_{40}H_{61}O_2N$ (Firbas), $C_{41}H_{71}O_2N$ (Davis), $C_{25}H_{39}ON$ (Colombano), $C_{34}H_{57}O_2N$ (Heiduschka and Sieger), forms needles,

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[1] *Jahresberichte*, 1820, **2**, 114.

[2] *Monats.* 1889, **10**, 541.

[3] *Ibid.* 1905, **26**, 445. *Cf.* Heiduschka and Sieger, *Arch. Pharm.* 1917, **255**, 18.

[4] *Compt. rend.* 1899, **128**, 887.

[5] *Pharm. Journ.* 1902 [iv], **15**, 160.

[6] *Gazzetta*, 1908, **38** [i], 19 ; 1912, **42** [ii], 101.

[7] *Jahresberichte*, 1820, **2**, 114.

[8] Zwenger and Kind, *Annalen*, 1859, **109**, 244 ; Schulz, *Zeit. Zuck-ind. Böhm.* 1900, **25**, 89 ; Zeisel and Wittmann, *Berichte*, 1903, **36**, 3554 ; Votoček and Vondraček, *ibid.* p. 4372 ; and Heiduschkla and Sieger, *Arch. Pharm.* 1917, **255**, 18.

m.p. 191° (Firbas), 205° (Davis), 214° (Colombano), from ether, and is soluble in warm alcohol, less so in ether. The salts crystallise badly. Solanidine gives the same colour reactions as solanine. It yields a diacetyl derivative, m.p. 203°.

Solaneine, $C_{52}H_{83}O_{13}N.3\frac{3}{4}H_2O$ (Firbas), $C_{48}H_{78}O_{13}N$ (Davis) was obtained by Firbas from potato embryos and by Davis from *Solanum Dulcamara*. It forms a horn-like mass, m.p. 208°, and is rather more soluble in hot alcohol than solanine. Like the latter, it is hydrolysed by acids into solanidine and a mixture of sugars.

Physiological Action of Solanine. Solanine closely resembles certain of the non-alkaloidal glucosides, such as the saponins, in action, but it is much less poisonous. The most characteristic property of these substances is their power of destroying red blood corpuscles. Sprouting potatoes are stated to contain more solanine than ordinary potatoes, and the consumption of these has occasionally given rise to symptoms of poisoning, such as headache, colic, vomiting and diarrhœa, accompanied by general depression.[1] The toxicity is also shown by the hydrolytic product solanidine.

Solanum Sodomeum

Solanine-S, $(C_{27}H_{48}O_9N)_2.H_2O$. This name has been applied by Oddo and collaborators to the solanine they have isolated from *Solanum sodomeum* by extracting the berries with 91 per cent. alcohol, filtering the liquors, acidifying with acetic acid, and then adding lime-water. The precipitate thus obtained on treatment with hot 80 per cent. alcohol gives a yield of solanine corresponding to 0·26 per cent. of the weight of berries used. This material is purified further by solution in dilute sulphuric acid, reprecipitating with alcoholic soda, and recrystallising repeatedly from 80 per cent. alcohol, from which it separates in aggregates of slender colourless needles, m.p. 245°–250° (*decomp.*), or from methyl alcohol in crystals, m.p. 275°–280°. The hydrochloride, B.HCl, forms microscopic scales, m.p. above 265°, and is insoluble in water. The aurichloride and platinichloride are microcrystalline. The colour reactions of solanine-S differ from those recorded for solanine from other sources. It gives with sulphuric acid a yellow colour changing to deep red, violet, and brown, and with alcoholic sulphuric acid a pale rose colour (not green, *see* p. 428). A solution of solanine-S when evaporated at 65°–70° with a few drops of platinic chloride solution

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[1] *Cf.* Wintgen, *Zeit. Nahr. Genussm.* 1906, **12**, 113.

gives a red colour changing to intense purple and violet if the heating is continued.[1] On hydrolysis by acids solanine-S gives solanidine-S, $C_{18}H_{31}ON$ (*see below*), along with galactose, dextrose and rhamnose. With acetic anhydride a deca-acetyl derivative is formed. Since solanidine-S (*see below*) contains its oxygen in the form of a hydroxyl-group and the nitrogen atom is present as an imino-group in it and the parent gluco-alkaloid, the structure of solanine-S may be represented thus, the arrows indicating the points at which hydrolysis occurs :

$$NH : C_{18}H_{29}.O - CHO[CHOH]_4(CH_2OH) - CH[CHOH]_4(CH_3) -$$

↑		↑
H		O
Solanidine	*Dextrose*	*Rhamnose*

$$O.CH[CHOH]_4(CH_2OH) - O.C_{18}H_{29} : NH$$

↑	
H	
d-*Galactose*	*Solanidine*
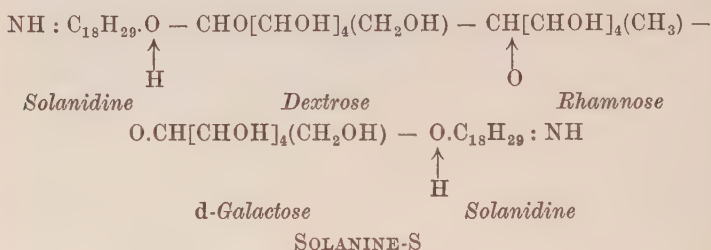
<div align="center">SOLANINE-S</div>

SOLANIDINE-S, $(C_{18}H_{31}ON)_3.2H_2O$ or $C_{18}H_{31}ON$, purified through the hydrochloride, forms nacreous, white scales, m.p. 197°–198°, $[\alpha]_D - 81° 23'$ (in benzene) from alcohol : it yields crystalline salts and an amorphous diacetyl derivative, $AcO.C_{18}H_{29} : NAc$,[2] due to the presence of an — OH and an : NH group.

<div align="center">*Solanum Angustifolium*</div>

From this plant Tutin and Clewer [3] have isolated a gluco-alkaloid which belongs to this group, but presents well-marked differences from any of those described above.

Solangustine, $C_{33}H_{53}O_7N.H_2O$, separates from hot amyl alcohol in pale yellow crusts of microscopic crystals, m.p. 235° (*decomp.*), and is only readily soluble in pyridine. It contains no methoxyl-group and its acetyl derivative could not be crystallised. The sulphate, $B_2.H_2SO_4.3H_2O$, forms small colourless needles, m.p. above 325°, and is only soluble, and that sparingly in boiling acetic acid. On hydrolysis solangustine yields one molecule each of dextrose and SOLANGUSTIDINE, $C_{27}H_{43}O_2N$. The latter is amorphous, but yields well-crystallised salts. The hydrochloride, B.HCl, forms lustrous

[1] *Gazzetta*, 1905, **35**, [i] 27 ; 1906, **36** [i], 310 ; 1911, **41** [i], 490 ; 1914, **44** [i], 680, 690 ; [ii], 191.
[2] Oddo, *loc. cit.* 1911, **41** [i], 534 ; 1914, **44** [ii], 191.
[3] *Trans. Chem. Soc.* 1914, **105**, 564.

plates, m.p. above 325°, from boiling alcohol containing hydrochloric acid. The nitrate, $B.HNO_3$, separates in colourless leaflets, m.p. 290° (*decomp.*) from alcohol by dilution with water. The picrate, yellow needles, has m.p. 250°. The monoacetyl derivative crystallises from ethyl acetate in colourless flattened needles m.p. 256°.

Other Solanum Spp.

From *Solanum grandiflorum* var. *pulverulente*, Freire,[1] in 1887, isolated a toxic alkaloid grandiflorine ; and *Solanum melongena*, the egg-plant, yielded to Yoshimura [2] trigonelline, β-amino-4-ethylglyoxaline and choline.

TAXUS BACCATA

Taxine, $C_{37}H_{51}O_{10}N$, is contained in the leaves, shoots, and fruits of the yew (*Taxus baccata*), from which it was first isolated by Lucas [3] in 1856. It was subsequently investigated by Marmé,[4] Hilger and Brande,[5] Amato and Capparelli, Thorpe and Stubbs,[6] and quite recently by Winterstein and collaborators,[7] and by Kondo and Amano.[8]

The alkaloid can be prepared by percolating powdered yew leaves with dilute sulphuric acid (1 per cent.), and exhausting this extract with ether after the addition of excess of dilute ammonia ; from the solution in ether the base is obtained by agitation with dilute acid and subsequent precipitation from the acid solution with ammonia. The crude alkaloid so prepared may be purified by solution in ether, filtration, and evaporation of the filtrate at ordinary temperatures.

Taxine, in the purest form in which it has yet been obtained, occurs in fine, glistening particles, m.p. 105°–110°, after sintering at 97°, $[\alpha]_D + 51\cdot5°$ in dry alcohol (W. and I.) ; $+ 35°$ (K. and A.). It is soluble in ether, chloroform, or alcohol, but is insoluble in water or light petroleum. The salts are all amorphous, including

[1] *Compt. rend.* 1887, **105,** 1074.
[2] *Journ. Chem. Soc. Japan,* 1921, **42,** 16 (*Chem. Soc. Abstr.* 1921 [i], 296).
[3] *Jahresberichte,* 1856, 550.
[4] *Bull. Soc. chim.* 1876 [ii], **26,** 417.
[5] *Berichte,* 1890, **23,** 464.
[6] *Trans, Chem. Soc.* 1902, **81,** 874.
[7] (With Iatrides) *Zeit. physiol. Chem.* 1921, **117,** 240 ; (with Guyer) 1923, **128,** 175.
[8] *J. Pharm. Soc. Japan,* 1922, 1074 (*Chem. Soc. Abstr.* 1923 [i], 361).

the aurichloride, m.p. 132°–134° (two forms, m.p. 90°–105°, 110°, K. and A.). The methiodide is amorphous, m.p. 123°—125°, and with alkali produces trimethylamine and a product, $C_{35}H_{44}O_{10}$, m.p. 120°-140°. Taxine, on reduction, takes up four atoms of hydrogen and forms a tetrabromide on addition of bromine. On oxidation with permanganate benzamide, benzoic acid, acetic acid, oxalic acid and benzonitrile are stated to be produced. Cinnamic acid seems to be a constant product of the action of alkalis and acids on the alkaloid.[1, 2] Warmed with dilute sulphuric acid for ten hours taxine yields a crystalline compound, $C_{11}H_{15}O_2N$, which may be a β-dimethyl-amino-β-phenyl-propionic acid.[1] Winterstein and Guyer [1] suggest the following formula from the observations so far made : $NMe_2.CHPh.CH_2.CO.C_{24}H_{34}O_6.OAc$. The alkaloid possesses a bitter taste, acts as a cardiac depressant, and interferes with respiration, so that death occurs from suffocation when it is administered to animals. It is said not to be poisonous to guinea-pigs.

Most of the work done on taxine has arisen out of poisoning cases among farm animals, and this aspect of the question is fully dealt with by Winterstein and Iatrides.[1]

VERATRUM SPP.

This group of alkaloids is obtained from products derived from various plants, of which the rhizomes of V. album and V. viride and the seeds of Schoenocaulon officinale are the most important. The two former are commonly known as white and green " hellebores " respectively, but are quite distinct from the true hellebores belonging to the natural order Ranunculaceæ. The alkaloids obtained from these sources are as follows :

1. Sabadilla seeds, Schoenocaulon officinale, A. Gray (Asagraea officinalis, Lindley), and perhaps also from Veratrum Sabadilla.

Cevadine (crystallised veratrine), $C_{32}H_{49}O_9N$.
Cevadilline (Sabadilline), $C_{34}H_{53}O_8N$.
Sabadine, $C_{29}H_{51}O_8N$.
Sabadinine = Cevine.
Veratridine (amorphous veratrine), $C_{37}H_{53}O_{11}N$.

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[1] (With Iatrides) Zeit. physiol. Chem. 1921, **117**, 240. (With Guyer) 1923, **128**, 175.

[2] J. Pharm. Soc. Japan, 1922, 1074 (Chem. Soc. Abstr. 1923 [i], 361).

2. White hellebore,
   Veratrum album (*V. Lobelianum*).

$\left\{\begin{array}{l}\textit{Jervine, } C_{26}H_{37}O_3N. \\ \textit{Pseudojervine, } C_{29}H_{43}O_7N. \\ \textit{Rubijervine, } C_{26}H_{43}O_2N. \\ \textit{Protoveratridine, } C_{26}H_{45}O_8N. \\ \textit{Protoveratrine, } C_{32}H_{51}O_{11}N. \\ \textit{Unnamed Base, } C_{26}H_{40}O_{10}N \text{ (?).}\end{array}\right.$

3. Green hellebore,
   Veratrum viride.[1]

$\left\{\begin{array}{l}\textit{Cevadine, } C_{32}H_{49}O_9N. \\ \textit{Jervine, } C_{26}H_{37}O_3N. \\ \textit{Pseudojervine, } C_{29}H_{43}O_7N. \\ \textit{Veratridine, } C_{37}H_{53}O_{11}N.\end{array}\right.$

4. *Veratrum nigrum.*   *Jervine,* $C_{26}H_{37}O_3N.$

Sabadilla Seeds

Cevadine, $C_{32}H_{49}O_9N$ (crystallised veratrine), was first isolated from sabadilla seeds by G. Merck [2] in 1855, who assigned to it the name veratrine and the formula, $C_{32}H_{52}O_8N$. The same alkaloid was subsequently obtained by Schmidt and Koppen,[3] and by Wright and Luff,[4] who in order to distinguish it from the mixture of amorphous bases sold in commerce as " veratrine " introduced the name " cevadine," which has been generally adopted, though Ahrens [5] suggested that it should be called " crystallised veratrine."

Wright and Luff prepared the alkaloid by percolating the finely powdered seeds with alcohol containing 1 per cent. of tartaric acid. The residue obtained by distilling off the solvent was poured into water to precipitate resin, the filtrate made alkaline with sodium carbonate and shaken out with ether ; from the ethereal solution the alkaloid was recovered by agitation with aqueous solution of tartaric acid. The purified solution thus obtained was again made alkaline and shaken out with ether, and from the latter the crystalline base was obtained by addition of sufficient light petroleum to produce a slight cloudiness and setting aside the mixture until precipitation occurred, after which cevadine (containing veratridine and cevadilline) separated and was recrystallised from warm alcohol by the addition of a little water. The yield was about 0·1 per cent.

The alkaloid crystallises in rhombic prisms with two molecules of alcohol,[6] which it loses at 130°–140°, m.p. 205° (anhydrous),

[1] Wright and Luff, *Trans. Chem. Soc.* 1879, **35**, 421.
[2] *Annalen,* 1855, **95**, 200.
[3] *Ibid.* 1877, **185**, 224.
[4] *Trans. Chem. Soc.* 1878, **33**, 338.
[5] *Berichte,* 1890, **23**, 2700.
[6] *Cf.* Freund and Schwarz, *ibid.* 1899, **32**, 800.

$[\alpha]_D^{17}$ + 12·5° (in alcohol), + 6·38° (in pyridine), + 1·25° (in acetone),[1] dissolves readily in hot alcohol, but is insoluble in water, and sparingly soluble in ether. The hydrochloride, B.HCl, crystallises in needles, and the aurichloride, B.HAuCl$_4$, from alcohol, in brilliant, yellow needles, m.p. 182° (decomp.). The platinichloride is amorphous and the nitrate crystalline. Cevadine gives a violet coloration with concentrated hydrochloric acid, which becomes red on warming. With sulphuric acid it becomes yellow, then red. Mixed with sugar and then moistened with sulphuric acid, a deep green colour, changing to blue, is produced.

Cevadine contains neither a methoxyl nor a methylimino group ; it forms an amorphous tetrabromide, yields crystalline benzoyl and o-nitrobenzoyl derivatives, m.p. 255° and 236° respectively, and a methiodide, which decomposes at 210°–212°, and is converted by silver oxide into cevadinemethylhydroxide.[2] When warmed with alcoholic soda, cevadine undergoes hydrolysis into cevine and angelic and tiglic acids. When hydrogen chloride is passed into cevadine in alcohol, ethyl tiglate and cevine are formed, so that tiglic acid does not seem to be produced from angelic acid first formed in this reaction.[3]

CEVINE, $C_{27}H_{43}O_8N.3\frac{1}{2}H_2O$, was first prepared by Wright and Luff [4] in an amorphous form, but was subsequently obtained crystalline by Freund and Schwarz.[5] It forms triclinic prisms, sinters at 155°–160°, melts at 195°–200°, $[\alpha]_D$ — 17·52° (in alcohol), reduces Fehling's solution, and with alcoholic potash forms a characteristic crystalline potassium derivative. The hydrochloride, B.HCl, crystallises in needles, m.p. 247° ; the aurichloride, m.p. 162° (decomp.) ; the methiodide, B.CH$_3$I.2H$_2$O, is crystalline and melts at 257°, and from it N-methylcevine, $C_{28}H_{45}O_8N.H_2O$, m.p. 277°, may be prepared. Dibenzoylcevine, m.p. 195°–196°, crystallises in large tablets ; diacetylcevine has m.p. 190°, and di-(o-nitrobenzoyl)-cevine, m.p. 175°, $[\alpha]_D$ — 54·7° (in alcohol).[6] On oxidation by hydrogen peroxide cevine forms cevine oxide,[7] $C_{27}H_{43}O_9N$, and on distillation with soda-lime, l-coniine is formed.[6]   Macbeth and

[1] Macbeth and Robinson, Trans. Chem. Soc. 1922, **121**, 1574.

[2] Frankfortes, Amer. Chem. Journ. 1898, **20**; 361.

[3] Horst, Chem. Zeit. 1902, **26**, 334.

[4] Trans. Chem. Soc. 1878, **33**, 338.   Cf. Ahrens, Berichte, 1890, **23**, 2702.

[5] Berichte, 1899, **32**, 800.

[6] Trans. Chem. Soc. 1922, **121**, 1574.

[7] Freund and Speyer, Berichte, 1904, **37**, 1946 ; Freund and Schwarz, J. prakt. Chem. 1917 [ii], **96**, 236.

Robinson [1] regard cevadine as a derivative of a substance, $C_{18}H_{30}O_4$, to which a coniine residue is attached *via* the nitrogen atom, thus :

$$(CHMe : CMe . CO . O)(HO)(- CO - O -)[C_{18}H_{25}O_4]N . C_5H_9Pr$$

        ↑   ↑

    (Tiglic acid residue)   *(Coniine residue)*
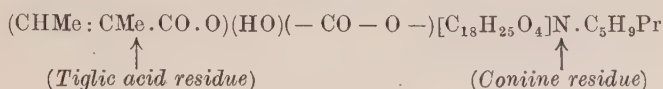
Cevadine is intensely poisonous. It stimulates the endings of the sensory nerves, giving rise to pricking sensations when applied to the skin and to violent sneezing if it comes into contact with the mucous membrane of the nose. It is owing to this action of this group of alkaloids that veratrum root is sometimes called " sneeze-wort." This irritation is followed by a sensation of numbness and cold. Cevadine has a characteristic action on muscle, intensifying the contraction and prolonging it. It at first stimulates the central nervous system, but in large quantities causes paralysis, terminating in failure of respiration. It resembles aconitine in its action on the circulation, but larger quantities are needed to produce the same effect. As in the case of aconitine and aconine, the removal of the acyl group from cevadine, with the production of cevine, results in a great fall in toxicity. The typical action of cevadine is retained, but in a much-weakened form in the monoacyl derivatives.

Veratridine (*amorphous veratrine*), $C_{37}H_{53}O_{11}N$. The name veratridine was first applied to this alkaloid by Bossetti.[2] The alkaloid appears to be identical with Schmidt and Koppen's water-soluble amorphous veratrine [3] from sabadilla seeds, and with the amorphous veratrine obtained by Wright and Luff [4] and by Merck [5] from the same source. The synonym " amorphous veratrine " is liable to be misunderstood, since commercial veratrine is amorphous and is the " total alkaloid " of sabadilla seeds.

Veratridine is the chief constituent of the amorphous precipitate produced on the addition of light petroleum to the solution of the total alkaloids of sabadilla seeds in ether, and is separated from the cevadilline also present by extraction with a small quantity of ether and purified by conversion into the characteristic, insoluble nitrate.

The alkaloid is an amorphous varnish-like substance, m.p. 180°. The nitrate is almost insoluble in water ; the sulphate, $B . H_2SO_4 . xH_2O$, forms fine needles. Alcoholic soda hydrolyses the

[1] *Trans. Chem. Soc.* 1922, **121**, 1574.
[2] *Arch. Pharm.* 1883, **221**, 82.
[3] *Berichte*, 1876, **9**, 1115.
[4] *Trans. Chem. Soc.* 1878, **33**, 341.
[5] *Annalen*, 1855, **95**, 200.

alkaloid into amorphous VERINE, $C_{28}H_{45}O_8N$, and veratric acid.[1]
Veratridine is a sternutatory, and as "amorphous veratrine" is
employed in medicine in neuralgic and similar complaints, its action
being almost identical with that of cevadine.

Cevadilline (*Sabadilline*), $C_{34}H_{53}O_8N$, is the amorphous residue,
insoluble in ether, obtained in the purification of cevadine. Its salts
are amorphous. When warmed with alcoholic soda, tiglic acid and
CEVILLINE, $C_{29}H_{47}O_7N$, are formed.[1] It has a physiological action
similar to but weaker than that of cevadine.

Sabadine, $C_{29}H_{51}O_8N$, was isolated by Merck [2] from sabadilla
seeds. It crystallises from ether in needles, m.p. 238°–240° (*decomp.*),
dissolves readily in alcohol or acetone, but is insoluble in light
petroleum. The hydrochloride, $B.HCl.2H_2O$, forms needles,
m.p. 282°–284° (*decomp.*), the nitrate, $B.HNO_3$, needles sparingly
soluble in water, and the aurichloride, $B.HAuCl_4$, fine golden-yellow
needles.

Sabadinine, also obtained by Merck from sabadilla seeds, was
shown by K. Hess and Mohr to be CEVINE [3] (p. 434).

White Hellebore

Jervine, $C_{26}H_{37}O_3N.2H_2O$, was first isolated from white helle-
bore in a pure state by Wright and Luff.[4] The alkaloid may be
recovered from the crude phosphate obtained as described under
protoveratrine, or better by mixing the dry ground rhizome with
barium hydroxide and water and extracting the mixture with ether,
which removes jervine, protoveratridine, and rubijervine. The
syrup left on distilling off the ether slowly deposits crystals of crude
jervine. On recrystallisation from dry alcohol protoveratridine
separates first. The partially purified jervine obtained in the later
fractions is digested with dilute sulphuric acid and so deposits the
nearly insoluble jervine sulphate, whilst rubijervine sulphate remains
in solution.[5]

Jervine crystallises from alcohol in stellate groups of long prisms,
m.p. 238°–242° (241°, Bredemann [6]); dissolves readily in alcohol,
chloroform, or acetone, but is less soluble in ether or light petroleum.

[1] *Trans. Chem. Soc.* 1878, **33,** 341.
[2] *Merck's Report,* 1890.
[3] *Berichte,* 1919, **52,** 1984.
[4] *Trans. Chem. Soc.* 1879, **35,** 405. *Cf.* Simon, *Ann. Chim.* [ii],
24, 214.
[5] Salzberger, *Arch. Pharm.* 1890, **228,** 462.
[6] *Apoth. Zeit.* 1906, **21,** 41, 53.

The hydrochloride, $B.HCl.2H_2O$, crystallises in four-sided prisms ; the nitrate, $B.HNO_3$, in hexagonal prisms, and the aurichloride, $B.HAuCl_4$, in golden-yellow prisms.   Jervine dissolves in sulphuric acid, forming a yellow solution which becomes green on warming.

The alkaloid depresses the circulation and is less irritating and far less poisonous than cevadine.

Pseudojervine, $C_{29}H_{43}O_7N$, was first obtained by Wright and Luff [1] and later by Salzberger, as described under protoveratrine. It crystallises from alcohol in hexagonal tablets, m.p. 300°–307° (304°, Bredemann), is slightly soluble in alcohol or benzene, but almost insoluble in light petroleum or ether.   It dissolves with a green colour in sulphuric acid.   The hydrochloride, $B.HCl.2H_2O$, and sulphate are crystalline, but the aurichloride is amorphous.

The alkaloid is stated to be physiologically inactive.

Rubijervine, $C_{26}H_{43}O_2N.H_2O$, also obtained by Wright and Luff and subsequently prepared by Salzberger, crystallises in prisms, m.p. 240°–246° (234°, Bredemann), somewhat resembling jervine. The alkaloid dissolves in sulphuric acid with a yellow colour passing into orange-red.   When warmed with hydrochloric acid it gives a reddish-violet coloration.   It is readily distinguished from jervine by the solubility of its sulphate in water.   It is not toxic.

Protoveratrine, $C_{32}H_{51}O_{11}N$, was first isolated by Salzberger, and is stated to be the substance to which the toxic properties of white hellebore are principally due.   It is prepared by percolating the finely-powdered drug with light petroleum to remove fat, and then with 80 per cent. alcohol.   The latter is distilled off under reduced pressure, the residual extract dissolved as far as possible in dilute acetic acid, and to the decanted clear solution metaphosphoric acid is added so long as any precipitate (insoluble phosphates of jervine and rubijervine) is formed.   The filtrate is made alkaline with ammonia and extracted first with ether and then with chloroform.   The ethereal extract on distillation leaves a crystalline residue of protoveratrine, which may be purified by recrystallisation from absolute alcohol.   The chloroform extract contains pseudojervine.

Protoveratrine crystallises in characteristic rectangular tablets, m.p. 245°–250°, and is sparingly soluble in chloroform, dry alcohol, or boiling ether.   The aurichloride, $B.HAuCl_4$, is an unstable crystalline precipitate.

[1] *Trans. Chem. Soc.* 1879, **35**, 405.   *Cf.* Simon, *Ann. Chim.* [ii], **24**, 214.

The alkaloid dissolves in sulphuric acid, giving a green colour passing into blue and violet. Hydrochloric and phosphoric acids give a cherry-red solution which slowly develops an odour of *iso*-butyric acid.

Protoveratrine resembles cevadine in physiological action, and is an even more potent heart-poison, but differs from it (1) in not prolonging muscular contraction, though it intensifies it ;[1] (2) in not ultimately paralysing the sensory nerve terminations, though, like cevadine, it at first stimulates them. It is more poisonous than cevadine. The lethal dose for rabbits by subcutaneous injection is 0·5 mg. per kilogramme of body weight.

Protoveratridine, $C_{26}H_{45}O_8N$, according to Salzberger, probably does not occur in the rhizome, but is formed by the action of barium hydroxide on protoveratrine (*see* p. 437). It crystallises in rectangular tablets, m.p. 265°, and is intensely bitter, but not poisonous. It gives a violet colour changing to red with sulphuric acid, and a carmine-red coloration with hydrochloric acid.

Bredemann [2] has obtained a sixth alkaloid, m.p. 239°–241°, crystallising in spherical aggregates of needles, but the remaining alkaloids of white hellebore have not been completely characterised.

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[1] *Cf.* MacNaughton, *Quart. Journ. Expt. Physiol.* 1913, **7,** 131.
[2] *Apoth. Zeit.* 1906, **21,** 41, 53.

MINOR ALKALOIDS OF UNKNOWN CONSTITUTION

Achillea Spp.

Achilleine, $C_{20}H_{38}O_{15}N_2$ (*A. Mille-folium*[1] and *A. moschata*).[2] Brown, amorphous, hygroscopic; peculiar odour and bitter taste; hydrolysed by dilute sulphuric acid to a reducing sugar, ammonia, and *achilletine*, $C_{11}H_{17}O_4N$; amorphous, bitter.

Moschatine, $C_{21}H_{27}O_7N$, from *A. moschata*.[2] Ill-defined gluco-alkaloid.

[1] Zanon, *Annalen*, 1846, **58,** 21.

[2] Von Planta, *ibid.*, 1870, **155,** 153.

Agaricus phalloides. . . . .

Kobert, *Abstr., Chem. Soc.,* 1900 [ii], 156.

Anacyclus Pyrethrum.

Resembles piperovatine (p. 50) . .

Dunstan & Garnett, *Trans. Chem. Soc.,* 1895, **67,** 100.

Anamirta paniculata.

Menispermine, $C_{18}H_{24}O_2N_2$. Rectangular prisms, m.p. 120°; readily soluble in alcohol or ether; sulphate crystalline.

Paramenispermine. Rectangular prisms, m.p. 250°; soluble in alcohol, sparingly in water or ether.

Both physiologically inactive.

Pelletier & Couerbe, *Annalen,* 1834, **10,** 198.

Anchusa officinalis.

Consolidine. Paralyses central nervous system.

Cynoglossine (B.HCl, crystalline). Paralyses peripheral nerves.

Greimer, *Arch. Pharm.,* 1900, **238,** 505.

Anona muricata.

Amorphous . . . . .

Callan & Tutin, *Pharm. Journ.,* 1911, [iv] **33,** 743.

Arachis hypogœa.

Arachine, $C_5H_{14}ON_2$, with choline and betaine. Yellowish-green syrup; crystalline platinichloride, m.p. 216°, and aurichloride; produces transient narcosis in frogs and rabbits with partial paralysis.

Mooser, *Landw. Versuchs-Stat.,* 1904, **60,** 321 (*Chem. Soc. Abstr.,* 1905 [i], 79).

Artemisia abrotanum.

Abrotine, $C_{21}H_{22}ON_2$. Crystalline, sparingly soluble in hot water; bitertiary base, sulphate (crystalline), and platinichloride.

Giacosa, *Jahresberichte,* 1883, 1356.

Atherosperma moschatum.
  Atherospermine, $C_{30}H_{40}O_5N_2$ (?). Amorphous, bitter powder, m.p. 128°; amorphous salts; evolves trimethylamine (?) on heating.

Zeyer, *Jahresberichte*, 1861, 769.

Bryonia dioica.
  Amorphous   .   .   .   .   .

Power and Moore, *Trans. Chem. Soc.*, 1911, **99,** 937.

Cassia Siamea.
  Alkaloid, $C_{14}H_{19}O_3N$.   Toxic   .   .

Wells, *Phil. Journ. Sci.*, 1919, **14,** 1.

A *Catha edulis* and B *C. palustris.*
  Katine,[1] $C_{10}H_{18}ON_2$.   Crystalline salts, sedative.
A { Cathine.   Crystalline.
     Cathidine.   Amorphous.
     Cathinine.   Crystalline sulphate.
     All act as nerve stimulants.[2]
B   Choline.[3]   .   .   .   .   .

[1] Chevalier, *Bull. Sci. Pharm.*, 1912, **18,** 264.
[2] Stockman, *Pharm. Journ.*, 1912, **89,** 676.

[3] Poulsson, *Arch. Exp. Path. Pharm.*, 1916, **80,** 173.

Ceanothus americanus.
  Two crystalline alkaloids, m.p. 255° and m.p. 200°.

Gordin, *Pharm. Rev.*, 1900, **18,** 266.

Cereus pecten aboriginum.
  Pectenine.   Crystalline hydrochloride, tetanising poison.

Heyl, *Arch. Pharm.*, 1901, **239,** 451.

Chloroxylon swietenia.
  Chloroxylonine, $C_{22}H_{23}O_7N$.   Colourless prisms, m.p. 182°–183°, $[a]_D^{18}$ — 9° 18'; B.HCl, m.p. 95°; B.HBr, m.p. 125°; B.HAuCl$_4$, m.p. 70°.   Contains four methoxyl groups, no hydroxyl.[1] Powerful irritant, causing dermatitis when applied to the skin.[2]

[1] Auld, *Trans. Chem. Soc.*, 1909, **95,** 964.
[2] Cash, *Brit. Med. Journ.*, Oct. 7, 1911.

Cimicifuga racemosa.   .   .   .   .

Finnemore, *Pharm. Journ.*, 1910 [iv], **31,** 142.

Cynoglossum officinale, Echium vulgare.
  Same constituents as *Anchusa officinalis.*

Gastrolobium calycinum.
  Cygnine, $C_{12}H_{22}O_3N_2$.   C o n v u l s a n t poison.

Mann & Ince, *Proc. Roy. Soc.*, 1907, **79,** B, 485.

Dictamnus albus.
  Dictamnine, $C_{12}H_{11}O_2N$.   Prisms, m.p. 132°–133°, B$_2$.H$_2$PtCl$_6$, m.p. 152°.

Thoms, *Ber. deut. Pharm. Ges.*, 1923, **33,** 68.

Erythrophleum Guineense (Sassy bark).

Erythrophleine, $C_{28}H_{43}O_7N$. Amorphous, hydrolysed by acids into methylamine and erythrophleic acid, $C_{27}H_{40}O_8$; heart-poison, resembling digitalin, and possesses local anæsthetic properties.

Gallois and Hardy, *Bull. Soc. Chem.*, 1876 [ii], **26**, 39.
Harnack, *Arch. Pharm.*, 1896, **234**, 561.
Power & Salway, *Amer. J. Pharm.*, 1912, **84**, 337.
Petrie, *Proc. Linn. Soc., N.S.W.*, 1921, **46**, 333 (occurrence in other species).

Fritillaria Imperialis.

Imperialine, $C_{35}H_{60}O_4N$. Colourless needles, m.p. 254°, $[a]_D$ — 35° 40′, B.HCl, crystalline; platinichloride and aurichloride amorphous. Both alkaloid and salts bitter; heart-poisons.

Fragner, *Berichte*, 1888, **21**, 3284.

Hymenodictyon excelsum.

Hymenodictyonine (*Hymenodictine*),[1] $C_{23}H_{40}N_2$.

No alkaloid present. [2]

[1] Naylor, *Pharm. Journ.*, 1882–83 [iii], **13**, 817; 1884–85 [iii], **15**, 195.
[2] Gibson & Simonsen (*Chem. Soc. Abst.*, 1918 [i], 151). Brill & Wells, *ibid.*, 1918 [i], 284.

Isopyrum thalictroides.

Isopyrine.

Mirande, *Compt. rend.*,1919, **168**, 316.

Larix decidua (*L. europœa*).

Tschirch & Weigel, *Arch. Pharm.*, 1900, **238**, 387.

Lolium temulentum.

Temuline, $C_7H_{12}ON_2$. Liquid, toxic.

Hofmeister, *Arch. exp. Path. Pharm.*, 1892, **30**, 203.

Lunaria biennis (*L. annua*).

Crystalline, m.p. 220°.

Hairs, *Bull. Acad. Roy. Belg.*, 1909, 1042.

Lunasia Spp.

Lunasine. Volatile .
Lunacrine   } Crystalline
Lunacridine }

Boorsma, *Meded. s'Lands., Planten.*,1899,**31**,13,126; *Bull. Inst. Bot. Buit.*, 1904, N. 31, pp. 8, 25.
Brill & Wells, *Phil. Journ. Sci.*, 1917, **12**, A, 167.

Lycopodium complanatum.

Lycopodine, $C_{32}H_{52}O_3N_2$. Monoclinic prisms, m.p. 114°–115°; B.2HCl. $2H_2O$ and B.2HAuCl$_4$; both crystalline.

Bödeker, *Annalen*, 1881, **208**, 363.

Lycopodium saururus.
  Pilijanine, $C_{15}H_{24}ON_2$.   Colourless
    needles, m.p. $64°-65°$; coniine-like
    odour; $B.H_2SO_4.\frac{1}{2}H_2O$,   rhombic
    prisms; $B.2H_2PtCl_6$,   glistening
    plates.   Toxic, causes convulsions
    and vomiting in dogs.

Adrian, *Compt. rend.*, 1886,
  102, 1322 ; and Arata &
  Canzoneri, *Gazzetta*, 1892
  [i], **22,** 49.

Mesembrianthemum expansum ("Channa").
  Mesembrine, $C_{16}H_{19}O_4N$.   Cocaine-like
    action.

Hartwich & Zwicky, *Apoth.
  Zeit.*, 1914, 29, 925 (*Chem.
  Soc. Abstr.*, 1915 [i], 710).

Myrtus Jambos (Eugenia Jambos).
  Jambosine. Crystalline, m.p. 77°.   .

Gerrard, *Chem. Soc. Abstr.*,
  1885, 396.

Nymphaea lutea (Nuphar luteum).
  Nupharine, $C_{18}H_{24}O_2N_2$.   Amorphous,
    physiologically inactive.

Grüning, *Berichte*, 1883, **16,**
  969.   *Cf.* Goris & Crété,
  Bull. Sci. Pharm., 1910,
  Jan.

Ormosia dasycarpa.
  Ormosine, $C_{20}H_{33}N_3$.   M.p. $85°-87°$,
    long needles with $3-4H_2O$. Methio-
    dide (abnormal), picrate, m.p. 178°
    (*decomp.*).
  Ormosinine, $C_{20}H_{33}N_3$. Prisms or cubes,
    m.p. 203°–205°. Methiodide, B.MeI,
    needles, m.p. 245°. Morphine-like in
    physiological action.

Hess & Merck, *Berichte*,
  1919, **52,** 1976.

Oryza sativa (Rice).
  Oridine, $C_5H_{11}O_2N$, $B.HAuCl_4$, m.p.
    277°; $B.HCl$, m.p. 240°. Crystalline,
    antineuritic when impure.

Hofmeister & Tanaka, *Bio-
  chem. Zeit.*, 1920, **103,**
  218.

Oxylobium parviflorum.
  Lobine, $C_{23}H_{31}O_4N_3$. Toxic.   .   .

Mann & Ince, *Proc. Roy.
  Soc.*, 1907, **79,** B, 485.

Palicourea rigida.
  Crystalline, m.p. 235°.   Toxic. .   .

Santesson, *Arch. Pharm.*,
  1897, **235,** 143.

Pentaclethra macrophylla.
  Paucine, $C_{27}H_{39}O_5N_5.6\frac{1}{2}H_2O$.   Yellow
    leaflets, m.p. 126° (*decomp.*); in-
    soluble in ether or chloroform.
    $B.2HCl.6H_2O$, colourless needles,
    m.p. 245°–247°; picrate, red prisms,
    m.p. 220° (*decomp.*); $B.H_2PtCl_6$.
    $6\frac{1}{2}H_2O$, m.p. 185°.   Furnishes di-
    methylamine when heated with po-
    tassium hydroxide ; toxic.

Merck's Report, 1894, p. 11.

Picea vulgaris (P. excelsa).   .   .   .

Tschirch & Brüning, *Arch.
  Pharm.*, 1900, **238,** 616.

Pilocereus sargentianus.
    Pilocereine, $C_{30}H_{44}O_4N_2$. Amorphous, m.p. 82°–86° ; toxic.

Heyl, *Arch. Pharm.*, 1901, **239,** 451.

Pinus pinaster. .   .   .   .   .

Tschirch & Brüning, *Arch. Pharm.*, 1900, **238,** 630.

Quebrachia Lorentzii.
    Loxopterygine, $C_{26}H_{34}O_2N_2$ (?). Amorphous, m.p. 81° ; amorphous bitter salts ; blood-red colour produced with nitric acid ; bluish-violet colour with sulphomolybdic acid.

Hesse, *Annalen*, 1882, **211,** 274. *Cf.* this book, p. 377.

Sarcocephalus Didderichii (West African boxwood).
    Cardiac poison   .   .   .   .

Gibson, *Biochem. Journ.*, 1906, **1,** 39.

Sinomenium diversifolium (S. acutum).
    Sinomenine, $C_{19}H_{23}O_4N$. Needles, m.p. 161° ; B.Cl, m.p. 231° ; picrate, m.p. 140°. Contains two methoxyl, one N-methyl and one hydroxyl group. Resembles quinine in action.
    Diversine, $C_{20}H_{27}O_5N$. Amorphous, m.p. 80°–93°. Contains two methoxyl, two hydroxyl and one N-methyl group.

Ishiwari, *Chem. Soc. Abstr.*, 1921 [i], 354 ; Kondo, Ochiai and Nakajima, *ibid.*, 1923 [i], 1222.

Skimmia japonica.
    Skimmianine, $C_{32}H_{29}O_9N_3$.   Yellow four-sided prisms, m.p. 175·5° ; readily soluble in alcohol or chloroform ; sparingly in ether. Salts crystalline. Bitter, poisonous to rabbits and frogs.

Honda, *Arch. exp. Path. Pharm.*, 1905, **52,** 83.

Spigelia marilandica.
    Spigeline. Liquid ; toxic. .   .   .

Dudley, *Amer. Chem. Journ.*, 1881, **1,** 150.

Stemona sessiliflora.
    Hodorine, $C_{19}H_{31}O_5N$. B.HBr, m.p. 258°–259° ; B.HCl, m.p. 244°–245°.

Furuya, *Chem. Soc. Abstr.*, 1913 [i], 1033.

Tabernanthe Iboga.
    Ibogaine, $C_{52}H_{66}O_2N_6$. Amber-coloured prisms, m.p. 152°, $[a]_D$ — 48·2° ; B.HCl, crystalline ; said to possess local anæsthetic properties, and, in large doses, to cause tetanus and convulsions.[1]
    Ibogine, $C_{26}H_{32}O_2N_2$, possibly identical with ibogaine.[2]

[1] Dybowsky & Landrin, *Compt. rend.*, 1901, **133,** 748.
[2] Haller & Heckel, *ibid.*, 1901, **133,** 850, 1236.

Tiliacora acuminata.

Tiliacorine, $C_{30}H_{27}O_3N(OMe)_2$. M.p. $260°$–$261°$, $[a]_D + 105\cdot3°$.

Van Itallie, *Pharm. Weekbl.*, 1922, **59**, 1381.

Tylophora Spp.

Tylophorine. Crystalline ; gives a play of colours with sulphuric acid.

Hooper, *Pharm. Journ.*, 1891, **21**, 6.
Greshoff, *Ber. Pharm. deut. Ges.*, 1899, **9**, 214.
Brill & Wells, *Phil. Journ. Sci.*, 1917, **12**, A, 167.

Valeriana officinalis. . . . .

Chevalier, *Compt. rend.*, 1907, **144**, 154.
Goris & Vischniac, *ibid.*, 1921, **172**, 1059.

Withania somnifera.

Amorphous alkaloid ; aurichloride, m.p. $185°$. Boiled with alcoholic potassium hydroxide, yields a crystalline base, $C_{12}H_{16}N_2$; leaflets, m.p. $116°$. Physiologically inactive.

Power & Salway, *Trans. Chem. Soc.*, 1911, **99**, 490.
Cf. Amer. Journ. Pharm., 1891, **63**, 77 ; Trebut, *Lancet*, 1886 [i], 467.

Zygadenus intermedius.

Zygadenine, $C_{39}H_{63}O_{10}N$. Needles, m.p. $200°$–$201°$, $[a]_D - 48\cdot2°$; toxic ; resembling cevadine in action.

Mitchell & Smith, *Amer. J. Physiol.*, 1911, **28**, 318 ; Heyl, Hepner & Loy, *Journ. Amer. Chem. Soc.*, 1913, **35**, 258.

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(Botanical names are printed in italics, and the principal reference to each subject is indicated by the page number in heavy type.)

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